Mayo Clinic Number

THE MEDICAL CLINICS
OF
NORTH AMERICA

Volume 13 Number 6

RELATIONSHIP OF BLOOD PRESSURE TO HEMORRHAGE IN PEPTIC ULCER IN MALES

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THE general conception of the pathologic process leading to hemorrhage in peptic ulcer is erosion of the wall of a blood vessel; either a large vessel may be affected, causing a sudden, frank hemorrhage, manifested by the appearance of blood in the vomitus and in the stool, and a systemic reaction, or there may be involvement of small vessels, which leads to oozing. If this conception is true, one can visualize a vessel that is weakened first by the sloughing of the supporting tissue around the wall of the blood vessel. One can visualize, also, a stage in which the wall of the vessel itself is involved in the ulcerative process, leading to lack of resistance to pressure of the blood from within.

It should be remembered that normal or increased pressure, by itself, does not cause the hemorrhage; this is occasioned by erosion of the wall of the vessel which permits any positive pressure from within to cause loss of blood.

In a previous paper Brown and I showed that patients with ulcer have a tendency toward hypotension rather than to hypertension. The present study began with examination of records of 1,809 surgically proved cases of peptic ulcer in The Mayo Clinic. Of these, 1,569 were in males. Only 21.2 per cent of the cases of ulcer occurred in females and in only 20.2 per cent of these had hemorrhage occurred. Hemorrhagic peptic

ulcer did not occur in females with sufficient frequency to warrant a comparison; therefore, the entire study was made from cases of surgically proved ulcers in males. The review was undertaken to ascertain whether patients with arterial hypertension had a greater tendency to bleed than those with arterial hypotension. No attempt was made to ascertain the factors leading to hypertension in the few cases in which the condition was associated with ulcer.

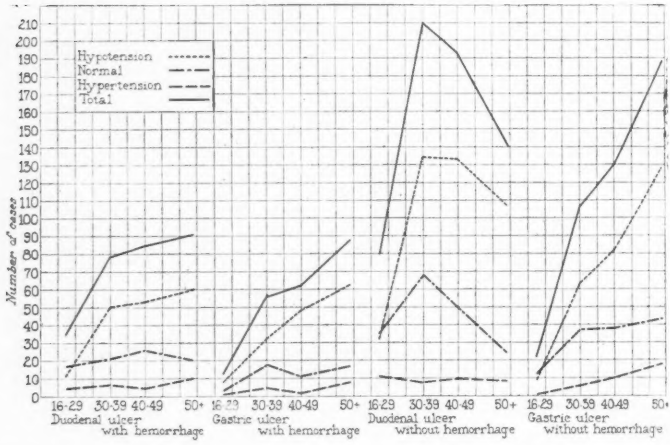

FIG. 191.—Incidence of hemorrhagic and nonhemorrhagic duodenal ulcer and of hemorrhagic and nonhemorrhagic gastric ulcer according to age groups.

The readings of blood pressure were taken as a part of the routine examination in the office. Tycos instruments and auscultatory technic were employed. These readings were taken at a time when the patient was not actually bleeding. The fact of the hemorrhage was established largely from the history, and occasionally from the surgical notes. The rising curve of blood pressure in males, coincident with advancing decades of life, as determined by Alvarez and Zimmermann, was accepted as the normal curve. To make allowance for individual variations, a range of 10 mm. on either side of this curve was taken.

Thus, a range of 20 mm. was allotted to individual variation. Any blood pressure reading occurring in a given decade, and falling within this allotted range, was classified as normal; those above, as indicating hypertension, and those below, hypotension.

With this division of readings of blood pressure it was found that the incidence of hypertension was so small as to make charting on a percentage basis precarious and results of such calculation are not given. Figure 191 deals with the total number of cases but by age groups in each of the four groups studied: hemorrhagic and nonhemorrhagic duodenal ulcer, and hemorrhagic and nonhemorrhagic gastric ulcer.

TABLE 1

BLOOD PRESSURE IN DUODENAL ULCER

Age group.	Cases.	Blood pressure.	Hemorrhagic cases.			Nonhemorrhagic cases.		
			Cases.	Per cent.	Probable error, per cent.	Cases.	Per cent.	Probable error, per cent.
16–29	113	Hypotension.	12	35.3	5.6	33	41.8	3.7
		Normal pressure.	17	50.0	5.8	35	44.3	3.8
		Hypertension.	5	14.7	4.1	11	14.0	2.6
30–39	288	Hypotension.	50	64.0	3.7	134	63.8	2.3
		Normal pressure.	21	27.0	3.4	68	32.4	2.2
		Hypertension.	7	9.0	2.2	8	3.8	0.9
40–49	276	Hypotension.	53	63.0	3.5	133	69.3	2.2
		Normal pressure.	26	31.0	3.4	49	25.5	2.1
		Hypertension.	5	6.0	1.7	10	5.2	1.1
50–	230	Hypotension.	60	66.7	3.3	107	76.3	2.4
		Normal pressure.	20	22.2	2.9	24	17.3	2.1
		Hypertension.	10	11.1	2.2	9	6.4	1.4

There were 286 cases of hemorrhagic duodenal ulcer available for study. These were divided according to age groups. Similarly, 621 cases of nonhemorrhagic duodenal ulcer which occurred over the same period of time as that allotted to the collection of the cases of hemorrhagic duodenal ulcer were divided according to age groups (Table 1).

The frequency of hypotension in patients with duodenal ulcer, both hemorrhagic and nonhemorrhagic, increases with advancing age, while the incidence of hypertension remains surprisingly low in the same group throughout all ages. Figure 192 discloses in a striking manner the parallelism of the three

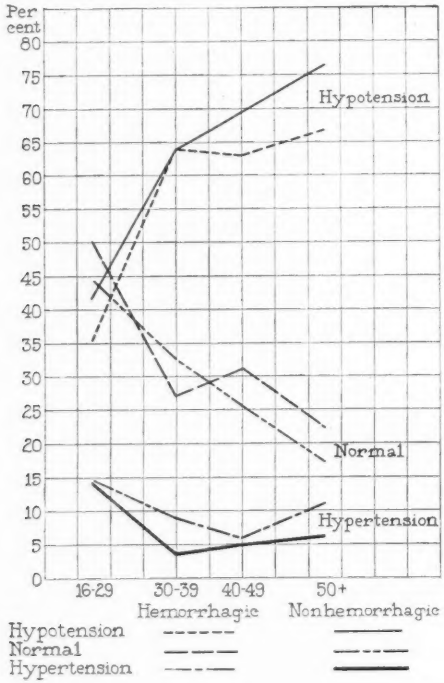

FIG. 192.—Parallelism of blood pressure in cases of hemorrhagic and of nonhemorrhagic duodenal ulcer.

divisions of blood pressure in hemorrhagic and nonhemorrhagic duodenal ulcer. It also emphasizes the relative infrequency of hypertension in either hemorrhagic or nonhemorrhagic duodenal ulcer.

Compilation of the figures for gastric ulcer shows close

parallelism of the blood pressure readings to those of duodenal ulcer. There were 215 cases of hemorrhagic gastric ulcer available for study, divided according to age groups. Four hundred forty-seven cases of nonhemorrhagic gastric ulcer were available for study, and these were classified according to age groups (Table 2). The increasing frequency of hypotension in advanc-

TABLE 2

BLOOD PRESSURE IN GASTRIC ULCER

Age group.	Cases.	Blood pressure.	Hemorrhagic cases.			Nonhemorrhagic cases.		
			Cases.	Per cent.	Probable error, per cent.	Cases.	Per cent.	Probable error, per cent.
16–29	34	Hypotension.	8	66.7	9.1	9	41.0	7.0
		Normal pressure.	3	25.0	8.4	12	54.5	7.1
		Hypertension.	1	8.3	5.6	1	4.5	3.0
30–39	161	Hypotension.	32	58.2	4.5	63	59.3	3.2
		Normal pressure.	18	32.7	4.2	37	35.0	3.1
		Hypertension.	5	9.1	2.6	6	5.7	1.5
40–49	191	Hypotension.	48	78.7	4.5	82	63.0	2.8
		Normal pressure.	11	18.9	3.5	38	29.2	2.7
		Hypertension.	2	3.3	1.5	10	7.7	1.6
50–	276	Hypotension.	62	71.3	3.2	128	67.7	2.3
		Normal pressure.	17	19.5	2.9	43	22.8	2.1
		Hypertension.	8	9.2	2.1	18	9.5	1.4

ing ages is again noted as well as the consistent infrequency of hypertension both in cases of the hemorrhagic and of the nonhemorrhagic groups. The parallelism of the three classifications of blood pressure in hemorrhagic and nonhemorrhagic gastric ulcer is not so close as in duodenal ulcer. However, these figures, when plotted, express the same trend as those of duodenal ulcer and illustrate just as strikingly the increasing frequency of hypotension in advancing decades and the constantly low frequency of hypertension (Fig. 193).

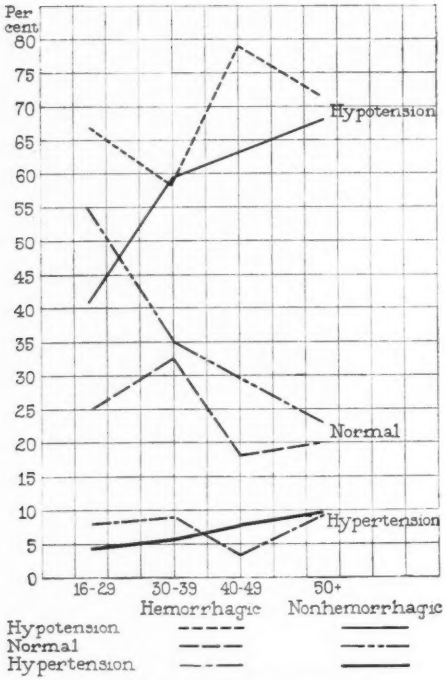

FIG. 193.—Parallelism of blood pressure in cases of hemorrhagic and of nonhemorrhagic gastric ulcer.

COMMENT

It would seem logical to assume that hypertension might predispose to hemorrhage in patients with peptic ulcer, because a blood vessel wall weakened by erosion of an ulcer would rupture more easily than one submitted to lower internal vascular pressure. Some alteration in the blood vessel probably occurs with any extravasation of blood, whether gastric, cerebral or otherwise. Marked hypertension is often tolerated by sound, or somewhat sclerotic vessels without hemorrhage; in other instances vascular insults occur with a moderate increase in vascular hypertension, which implies lack of resistance of the vascular wall.

In the cases of hemorrhagic duodenal ulcer in males, at all ages from sixteen to fifty, the numerical incidence of arterial hypertension, according to the standard adopted, was 27 in 286, whereas in the cases of nonhemorrhagic duodenal ulcer in males of the same age groups, the numerical incidence of hypertension was 38 in 621. In the cases of hemorrhagic gastric ulcer in males in all age groups from sixteen to fifty the numerical incidence of hypertension was 16 in 215, and in the cases of nonhemorrhagic gastric ulcers from the same groups, the incidence of hypertension was 35 in 447. This study seems to indicate that hypertension is not a contributing factor in the causation of hemorrhage in either gastric or duodenal ulcer.

TWO CASES OF SECONDARY TUMOR OF THE HEART IN CHILDREN, IN ONE OF WHICH THE DIAGNOSIS WAS MADE DURING LIFE

FREDRICK A. WILLIUS AND SAMUEL AMBERG

FROM time to time secondary tumors are found involving the heart, their presence invariably being accidental discoveries at the time of necropsy. Bryant, in 1907, reviewed 2,942 necropsies, and discovered only nine cases of metastatic tumors of the heart: One case of sarcoma, one case of lymphosarcoma, two cases of epithelioma, one case of endothelioma, and four cases of carcinoma. A similar incidence of metastatic tumors of the heart was noted by Karrenstein, who, in an analysis of 6,655 necropsies, found nineteen cases. Fifteen of these were carcinomas and four were sarcomas.

Goldstein, in a comprehensive review of the literature, noted only 150 authentic cases, emphasizing the rarity of the condition. These cases will not be considered here, since we are concerned only with secondary tumors. Several cases of primary cardiac tumors have been reported in children. As far as secondary sarcoma of the heart is concerned, Goldstein was of the opinion that many occur that are never recorded in the literature.

Among the references to cases in Goldstein's article, the age of the patient is not always recorded, but in one case a large round-cell metastatic sarcoma of the heart was described in a boy, aged eight years. The primary growth apparently was situated in the sternal periosteum. Another case is that reported by Grawitz, in which a lymphosarcoma originating in the thymus gland involved the myocardium by direct extension. The patient was a girl, aged twelve years.

We have not attempted a complete survey of the literature on the subject.

It is unusual to find sufficient clinical evidence occurring in a proper sequence to permit the diagnosis of metastatic tumor of the heart prior to death. We were accorded such an opportunity in the following case:

Case I.—A girl aged eight years was brought to The Mayo Clinic, March 16, 1927 because of pain and swelling in the region of the left knee. The child was a twin; birth and infancy had been normal. She had had scarlet fever a year and a half previously, and two months later an acute infectious illness that was said to be influenza. There had been several attacks of acute tonsillitis for which tonsillectomy had been performed. Four weeks prior to examination in the clinic, the child complained of pain in the left knee, and slight swelling in this region was noted. Slight limp was observed at this time. On further questioning, the child's mother recalled the fact that pain had first occurred three months previously, but little, if any, attention was paid to it. It occurred intermittently, and several days would elapse during which the child appeared to be entirely free from pain. The family physician had been consulted one month before and had advised complete rest in bed for a period of a week, which was carried out without relief of symptoms. During this time the temperature ranged from 101° to 102° F. Other joints were not involved.

The patient was undernourished and pale. She weighed 42.5 pounds. The left knee was approximately 2.5 cm. larger in circumference than the right; the motion was not limited but movement of the joint caused considerable pain.

The systolic blood pressure was 80 and the diastolic pressure 60. The pulse rate was 108 and temperature 100° F. Urinalysis was negative except for a faint trace of albumin. The hemoglobin was 73 per cent (Dare). Leukocytes numbered 8,800. The Wassermann reaction of the blood was negative. Examination of the ear, nose, and throat did not reveal abnormalities; the tonsils had been cleanly removed. A roentgenogram of the thorax was negative; that of the left knee showed a destructive process of the outer aspect of the lower third of the femur with considerable elevation of the periosteum. A diagnosis of bone tumor or osteomyelitis was made and exploratory operation was advised.

March 20, 1927, at exploration of the lower portion of the left femur, a bloody mass of tissue was encountered from which specimens were obtained for microscopic study. The femur was roughened, and an area of actual destruction of bone occurred along the lower and outer space. Microscopic study of the tissue removed revealed an endothelioma of the Ewing type (sarcoma).

March 24, the first roentgen-ray treatment was given: 135 kilovolts at a distance of 40 cm. with 5 milliamperes for eighteen minutes. The child's convalescence was uncomplicated and she was allowed to return home at the end of three weeks.

The child was observed again, April 28, at which time her condition appeared to be satisfactory. Roentgenograms of the left femur still showed

marked destruction of the lower third with periosteal perforation. A second roentgen-ray treatment was given on this day, identical to the first treatment. June 29, examination disclosed further satisfactory improvement. Roentgen-ray examination of the thorax was negative. The third roentgen-ray treatment was given July 1, and the fourth treatment July 28.

October 12, the child was examined again; she appeared to be perfectly well. Roentgenograms of the thorax did not reveal abnormalities. The fifth and final roentgen-ray treatment was given.

December 6, examination revealed the child to be in good condition and the leg, to appearance and palpation, was normal. A roentgenogram of the left femur was identical with the previous ones. Roentgenograms of the thorax did not show abnormalities.

The child returned for further observation, February 23, 1928, and was found to be in good condition. Roentgenograms of the left femur and of the thorax were the same as on the previous examinations. September 4, the patient complained of stiffness of the left leg. The leg appeared to be somewhat mottled, but otherwise appeared to be normal. A roentgenogram of the skull and of the lumbar portion of the spinal column did not reveal abnormalities, and the left femur was as it had been on previous visits.

The next examination was made April 4, 1929. At this time the mother stated that the child was observed to fatigue easily. During the last six months increasing periods of rapid action of the heart and shortness of breath had been noted, and during this time the patient had lost 9 pounds in weight. During the last month the child had become quite blue, and slight exertion caused marked shortness of breath.

There was a moderate degree of cyanosis. The heart was markedly enlarged, the apex beat being visible in the fifth intercostal space, 10 cm. from the midsternal line. The rhythm of the heart was regular, but the rate was rapid. The presence of a loud blowing systolic apical murmur was noted. Urinalysis revealed a faint trace of albumin and the presence of an occasional leukocyte. The hemoglobin was 76 per cent (Dare); the erythrocytes numbered 5,280,000 and the leukocytes 9,400. Roentgenograms of the heart showed it to be markedly enlarged, both to the right and to the left. The left femur showed increased density at the site of the old lesion. Electrocardiographic examination revealed the presence of incomplete bundle-branch block, T-wave negativity in leads II and III, slight elevation of the R-T segment in leads I and II with a corresponding depression in lead III. A moderate degree of right ventricular preponderance was evident. The diagnosis at this time was cardiac tumor, secondary to the original tumor of the left femur (Ewing type of endothelioma).

The child was again observed May 7, 1929, at which time the condition did not show material change. Reduplication of the apical first sound was noted. The electrocardiogram was identical to the previous tracing. The only change noted on examination was greater cardiac enlargement, which was verified by the roentgenogram. The electrocardiogram at this time showed complexes of lower amplitude, particularly in leads II and III, and the R-T segment showed greater elevation in lead I, while depression of the segment occurred in leads II and III, and was especially evident in lead III.

FIG. 194.—The left ventricle is embedded in the right ventricle and has well preserved muscular walls.

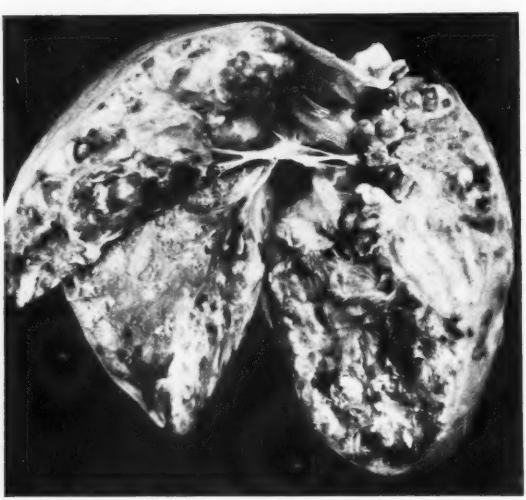

FIG. 195.—The right ventricle is opened; the remnant of the right chamber of the heart and the extensive tumor can be seen.

July 28, the patient was seen at her home in a neighboring town, in a critical condition. Ascites and marked edema of the extremities were present, and the cardiac dulness extended well into the midaxilla. The cardiac tones were of poor quality and distant. She died August 30.

At necropsy the heart weighed 450 gm. (Figs. 194, 195). The left ventricle appeared normal and appeared to lie in the concave side of an enormously enlarged right ventricle which bulged around it. When the heart was opened, the cavity of the right ventricle was found to be confined to an extremely small space; the greater portion of the right ventricle was tumor. The only area of the right ventricle that was not involved by the tumor was the right anterior portion of the conus. A small metastatic nodule, 2 cm. in diameter, was found in the median portion of the upper lobe of the right lung. The tumor of the heart and the nodule of the lung were identical to the original tumor of the left femur and were identified as the Ewing type of endothelioma (sarcoma).

This case was of unusual interest in that the occurrence of the various events during our rather prolonged period of observation created a fairly definite clinical picture which permitted us to venture the diagnosis of secondary cardiac tumor. The philosophy of our diagnosis is found in the following sequence of events. The first examination of the child, conducted March 16, 1927, did not reveal evidence of cardiac disease as shown by general examination and by the roentgen ray. Positive histopathologic evidence of a malignant tumor of the left femur was obtained at this time. During the succeeding eleven months the child was repeatedly examined and no evidence of cardiac involvement was determined subjectively, objectively, or by means of the roentgen ray. The first cardiac symptoms became evident in November, 1928, twenty-one months after our initial examination of the patient, and during this time the patient was not subject to any acute infectious illness to which cardiac involvement could be attributed. Our next opportunity to examine the patient occurred April 4, 1929, at which time marked evidence of cardiac failure was apparent and the heart, both by general examination and by the roentgen-ray examination, was markedly enlarged. The electrocardiogram obtained at this time (Fig. 196) disclosed a distinct adult type of curve, which has been shown by Barnes to indicate infarction of the posterior surface of the left ventricle; this region in most normal hearts is supplied by the right coronary artery.

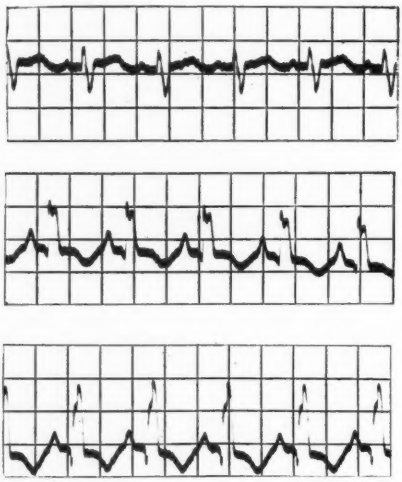

FIG. 196.—Electrocardiogram taken April 4, 1929; incomplete bundle-branch block with T-wave negativity in leads II and III; slight elevation of the R-T segment in leads I and II, with a corresponding depression in lead III; moderate degree of right ventricular preponderance.

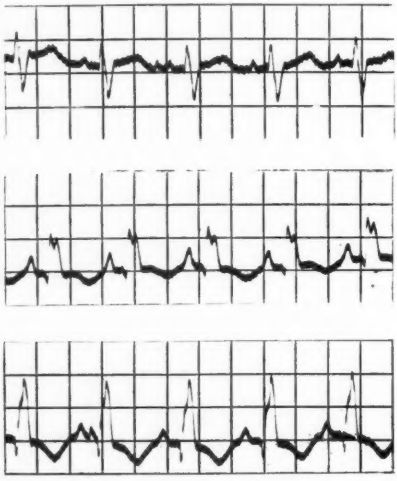

FIG. 197.—Electrocardiogram taken May 7, 1929; identical with that shown in Figure 196.

With these facts at hand we felt justified in venturing the diagnosis of secondary tumor of the heart. From the electrocardiographic evidence we were unable to conclude positively whether the involvement was on the right or the left side, but

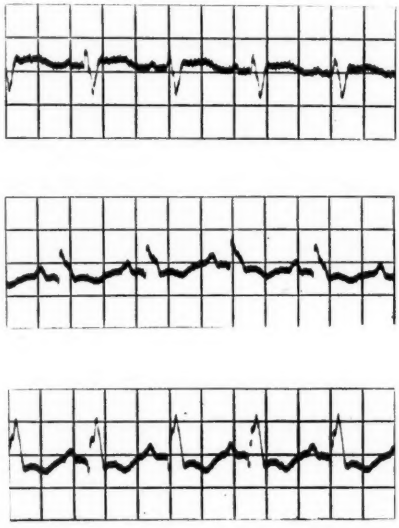

FIG. 198.—Electrocardiogram taken July 8, 1929; complexes of lower amplitude, particularly in leads II and III, and elevation of the R-T segment more pronounced in lead I, while depression of the segments occurred in leads II and III, especially evident in lead III.

involvement of the right ventricle seemed most likely. Other observers have found the right side of the heart involved by metastatic tumor more commonly than the left (Figs. 197, 198).

Case II.—A boy aged two and a half years had had his tonsils and adenoids removed on account of anemia about eight months before admission. Protrusion of the eyes occurred with an attack of pertussis about four months later, but the protrusion did not recede with subsidence of the attack, and a sinus operation was performed without benefit. Later the eye sockets were punctured with needles, but pus was not found. The protrusion of the eyeballs progressed and the head became greatly swollen. Roentgen-ray treatments were given, and recession of the eyes and swelling resulted. Trans-

fusions, and leukocytic and liver extract were given. Two weeks before admission, swelling of the right jaw was noted and the respiration became rapid and dyspneic. Before roentgen-ray treatment the leukocytes numbered 15,600; later they numbered 6,000; the number of erythrocytes was not much decreased.

The patient arrived at the clinic with the diagnosis of leukemia. The temperature was 101° F., the hemoglobin was 40 per cent, the erythrocytes numbered 3,000,000 and the leukocytes numbered 152,000, with 97 per cent lymphocytes, and many immature cells. The left eyeball protruded. Liver,

FIG. 199.—Anterior aspect of heart; considerable distortion is shown, which was caused by the tumors.

spleen, and heart were enlarged, and the left lower side of the thorax was dull to percussion. An emergency roentgen-ray examination showed considerable enlargement of the heart and infiltration of the lungs. Clinically the dyspnea was the outstanding feature, so radium was applied over the thorax, but the child died less than twenty-four hours after his arrival.

At postmortem examination leukosarcoma was found in many organs, of which only the heart claims our interest here. The epicardial surface of the heart was covered with fibrinous exudate and it was irregularly nodular due to invasion of a tumor into the epicardium. The nodules were white and

firm, and measured 0.5 to 3 cm. in diameter, but due to fusion were not always sharply defined throughout. Many of the nodules invaded the myocardium, some almost penetrating through to the endocardial surface. Figures 199 and 200 show the masses of tumerous tissue. The right ventricle, the apex, the posterior surface of the left ventricle, and the basal regions were involved rather extensively.

FIG. 200.—Posterior aspect of heart.

A similar case has been cited by Mönckeberg, who did not give the age of the patient. His case was a case of acute lymphatic leukemia, and the cells, as in our case, were small lymphocytes and large cells resembling lymphoblasts; many of the cells in our case contained mitotic figures.

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ANGINA PECTORIS ASSOCIATED WITH EXOPHTHALMIC GOITER AND HYPERFUNCTIONING ADENOMATOUS GOITER*

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THE association of hyperthyroidism and angina pectoris is not common. When it occurs, it involves factors in prognosis which do not correspond with other criteria in these two conditions. For this reason, we have undertaken to trace a group of patients in whom these two conditions were present. In the literature there appear a few reports of cases of hyperthyroidism complicated by angina pectoris and reports of relief of angina after an exophthalmic goiter or hyperfunctioning adenomatous goiter has been successfully operated on. Lev and Hamburger reported six such cases, in four of which relief of angina followed partial thyroidectomy. Sturgis likewise reported a case of exophthalmic goiter and angina pectoris in which the latter condition was relieved following partial thyroidectomy. Hurxthal analyzed 500 cases of cardiac failure in hyperthyroidism and found among them two patients with angina pectoris. Means, White, and Krantz reported an increase in the severity of angina pectoris in some cases coincident with the elevation of the basal metabolic rate by the administration of thyroid preparations. We have not attempted to determine the relative incidence of angina pectoris in association with the hyperthyroid states in patients seen at The Mayo Clinic. In all probability, the frequency of the association is slightly higher than is ordinarily supposed, as it is very easy to overlook angina pectoris in the presence of severe hyperthyroidism, or mild hyperthyroidism in a patient with angina pectoris.

* Read by title before the Central Society for Clinical Research, Chicago, Illinois, November 22, 1929.

It is not our purpose in this paper to enter into the various considerations regarding the pathologic physiology of angina pectoris. The term "angina pectoris" is used in the same sense as it is used by Heberden in his original description of the disease.

The mechanism by which an increase in the basal heat production in the body, as induced by hyperthyroidism, results in cardiac embarrassment has not been conclusively demonstrated. We lean to the view that an elevation of the basal metabolic rate results in an increased minute volume output from the heart (which, as stated by Boas, may be 25 to 60 per cent above normal) and that angina pectoris is largely the result of an inadequate supply of blood to satisfy the needs of the cardiac musculature for the moment. It is easy to conceive, then, of a heart, the coronary blood supply of which is sufficient under normal circumstances, but is inadequate to meet the demands placed on it by the added work of the heart produced by hyperthyroidism. Whitten has shown in his injected preparations that there is great variability in the coronary circulation and that some apparently normal hearts may have a relatively small blood supply through the coronary arteries. Such hearts might withstand the stress of hyperthyroidism less well than hearts with a greater coronary circulation. Willius, Boothby, and Wilson have called attention to the increase in the rate of blood flow in hyperthyroidism, and the resultant increase in the work of the heart. Davies, Meakins, and Sands found in patients with hyperthyroidism an increased minute volume output of the heart; the increase is relatively proportional to the increase in basal metabolic rate. After thyroidectomy the minute volume output of the heart dropped to normal and the output of the heart per beat diminished. Liljestrand and Senström found an increased minute volume output from the heart in exophthalmic goiter. They felt that this fact accounted for the increased work of the heart in exophthalmic goiter and that the strain on the heart was dependent on the increased work. Robinson and Burwell also found greatly increased cardiac output in a case of hyperthyroidism. Various theories have been proposed to explain the effect of hyperthyroidism on the heart. Boas has

suggested that the greatly increased blood supply through the thyroid gland acts as a shunt and has the same effect as arteriovenous aneurysm in increasing the work of the heart. Hurxthal feels that the flabby heart seen in exophthalmic goiter probably is produced by the same mechanism as the changes in skeletal muscles and that the weakness which results is the cause of the cardiac disturbance. It seems probable that hyperthyroidism does have some effect on the myocardium, more than that explained by increased work. However, it is not necessary to assume this in relation to the cases in the present study inasmuch as we know that the actual work of the heart is increased in hyperthyroidism.

Thirty-three patients who had both angina pectoris and hyperthyroidism were studied. Seventeen of the patients had exophthalmic goiter, and sixteen, hyperfunctioning adenomatous goiter. There were sixteen males and seventeen females. Partial thyroidectomy was performed on twenty-eight of the patients. Of the five that did not receive surgical treatment, two had exophthalmic goiter and were treated with compound solution of iodine; three had hyperfunctioning adenomatous goiter and did not receive specific medical treatment. Four of these five patients are dead, and the other patient is having increasingly severe angina. Of the twenty-eight patients on whom partial thyroidectomy was performed, none reported symptoms indicating a recurrence of hyperthyroidism and none of those reexamined had evidence of hyperthyroidism. This, then, presents an ideal group in which to study the effect exercised by the control of hyperthyroidism on angina pectoris. Three patients who were treated by partial thyroidectomy were dead at the time of this study. One of these died in an anginal seizure on the day of the operation; one died four months after operation from angina pectoris, and one died four years after operation, of an unknown cause.

The average time that elapsed between operation and the subsequent observation in the twenty-five cases in which the patients are living in this group (surgical) was twenty-six months. The shortest time was four months, and the longest,

eighty-four months. In five cases the angina pectoris preceded the hyperthyroidism; in thirteen, the opposite was true, and in the remainder the two diseases were so close together in onset that they could not be separated on historic evidence.

Twenty-three of the twenty-five patients reported lessening in the severity of angina after thyroidectomy. In the other two cases angina was present in about the same degree as before operation. In eight cases the improvement in angina was reported as very great. All patients were, of course, advised in regard to restriction of physical activity; this factor cannot be measured in relation to the reduction in anginal pain. However, in no case was improvement noted except when the patient stated that he could perform greater exertion without production of pain than had been the case before operation. Three of the patients who reported marked lessening of angina had had a very severe degree of angina before thyroidectomy.

In ten of the cases in the entire group significant inversions of the T wave were shown in electrocardiograms. In five cases the T wave was inverted in lead 1, in two cases in leads 1 and 2, in one case in leads 1, 2, and 3, in one case in leads 2 and 3, and in one case a diphasic T wave in lead 1 was associated with an incomplete bundle-branch block and auricular fibrillation. Seven patients had auricular fibrillation and in five of these this was the only electrocardiographic abnormality. In one case there was paroxysmal nodal tachycardia. In the ten cases in which there were significant inversions of the T wave in the electrocardiogram, five patients are dead. In three cases the angina is less severe, in one case there is no definite improvement, and one patient who did not undergo thyroidectomy has more severe angina. Of the five patients who had auricular fibrillation as the only abnormality notable in the electrocardiogram, the angina was markedly improved following thyroidectomy in three instances, slightly improved in one instance, and one patient is dead. Two patients with auricular fibrillation, who also had significant inversion of the T wave, report their angina improved.

Of the group of thirty-three patients, seven were dead at

the time of this study. Reference already has been made to those patients who died following surgical operation. Of the four patients who died without operation, one patient refused operation and died two years after observation; one was advised not to be operated on because of associated arteriosclerosis of the central nervous system, with dementia; one died of cardiac decompensation two years after refusing thyroidectomy, and one died in an anginal seizure twenty-one months after observation. The last patient, who had exophthalmic goiter, had experienced great relief from angina following treatment with iodine, but later had showed steady progression of the angina. The following illustrative cases are reported.

Case I.—A man aged forty-nine years came under observation in May, 1927. He had lost weight for two years and for the same time had had dyspnea on exertion, tachycardia, and loss of strength. For one and a half years he had had substernal pain which had come on during exertion and especially after large meals. The pain had radiated to the left arm.

At the time of examination the patient's appearance was that of a man moderately stimulated and with a fine tremor of the fingers. There was a stare characteristic of exophthalmic goiter. The thyroid gland was slightly enlarged; each lobe was about 4.5 cm. long and 3.5 cm. wide. The heart was enlarged to a total transverse diameter of 16 cm. The blood pressure was 170 systolic and 80 diastolic measured in millimeters of mercury. The basal metabolic rate was +48 per cent. Other examinations gave essentially negative results. The patient was kept in bed, and compound solution of iodine, ten minims three times daily, was given. He had at least one attack of angina pectoris daily. After sixteen days partial thyroidectomy was done and the pathologists reported the tissue removed as "hypertrophic parenchymatous thyroid." During the immediate convalescence one attack of angina pectoris occurred, and after dismissal from the hospital another attack followed moderate exertion.

In October, 1927, the patient was seen again. He had not had precordial pain since the previous observation. The auricles were fibrillating. The basal metabolic rate was −19 per cent. In February, 1928, at the last observation, there had not been a recurrence of angina pectoris. There was moderate dyspnea on exertion. Electrocardiographic examination showed auricular fibrillation alternating with auricular flutter.

Case II.—A man aged fifty-nine years was examined in March, 1925. Eight years before, he had had an illness during which exophthalmos had developed. He had lost 65 pounds in weight and had been bothered by rapidly beating heart. Seven years previously he had been found to have a systolic blood pressure of from 200 to 230. Six months before our exam-

ination he had had an attack of pain in the epigastrium and substernal region, which had been referred to the left arm. The attack had lasted forty minutes and had been relieved by inhalation of amyl nitrite. Following this, there had been frequent attacks, chiefly after exertion but occasionally when he was quiet. There had been dyspnea on the slightest exertion. Edema of the eyelids had been noted for three months.

On examination the systolic blood pressure was 190 and the diastolic pressure, 110. There was a systolic murmur over the aortic area. The total transverse diameter of the heart measured 18.25 cm. in a teleoroentgenogram. The edge of the liver was palpable 4 cm. below the costal margin. Electrocardiographic examination showed a cardiac rate of 94 beats for each minute, auricular premature contractions, left ventricular preponderance, and an inverted T wave in lead 1. Because of slight tremor, a warm, moist skin, and a previous history indicating exophthalmic goiter, the basal metabolic rate was determined and found to be +42 per cent. Compound solution of iodine was given and the basal metabolic rate fell after sixteen days to +14 per cent. The anginal attacks were much less frequent and severe after the iodine effect had been obtained, and the patient was able to move about his room without discomfort. Long walks, however, were followed by anginal attacks of much less severity than he had previously had. Thyroidectomy was advised but was refused by the patient.

The patient returned home and continued to take iodine. His sister reported later that he had been much better for several months, that the anginal attacks had then gradually increased in frequency and severity and that he had dropped dead in a hotel lobby nineteen months after he had first come under our observation.

Case III.—A woman aged sixty-two years was examined in May, 1925. She had been ill for two years, with rapidly beating heart, intolerance to heat, intermittent diarrhea, rapid loss of weight (40 pounds), and weakness. The severity of the symptoms had fluctuated. For one year she had been subject to dyspnea, edema of the ankles, and increasing tachycardia and weakness. During this time she had had attacks of pain over the precordial region, referred to the left arm, coming on during exertion. More recently the attacks of pain had followed such slight exertion as moving about in bed.

Examination revealed moderate restlessness, edema of the eyelids of the type seen in exophthalmic goiter, and a stare. The thyroid gland was diffusely enlarged; each lobe measured about 6.5 cm. in length by 2.5 cm. in width. There were bruits at the superior poles. The heart was slightly enlarged; the total transverse diameter was 14 cm. The auricles were fibrillating. There was moderate edema of the ankles. The finger nails were undermined at the distal edges, as they frequently are with exophthalmic goiter. The basal metabolic rate was +58 per cent. Electrocardiographic examination revealed a ventricular rate of 120 beats each minute, auricular fibrillation, and slurring of the QRS complex in lead 3. Ten drops of compound solution of iodine were given three times daily. The attacks of precordial pain became less frequent and severe. After nine and fourteen days respectively the basal metabolic rates were +17 per cent and +16 per cent.

Partial thyroidectomy was done one month after admission. The tissue removed was characteristic of diffuse parenchymatous hypertrophy. Convalescence was uneventful.

In answer to a questionnaire sent two and a half years later, the patient wrote that for two years she was entirely free from precordial pain and had been able to exert herself moderately. During the last six months before the time when she wrote to us there had been recurrence of precordial pain following exertion but not of such severe degree as had been present at the time of the original examination.

CONCLUSIONS

Cases of angina pectoris complicated by exophthalmic goiter or hyperfunctioning adenomatous goiter show, in most instances, definite improvement in the angina following control of the hyperthyroidism by partial thyroidectomy. The risk of partial thyroidectomy in these cases is not so great as to contraindicate its use, even in patients with severe angina, as in some instances striking relief of angina is obtained. Inasmuch as the removal of added work from the heart is of paramount importance in patients with angina pectoris, prompt control of hyperthyroidism by thyroidectomy offers the most efficient means of treatment in patients who have both conditions. The prognosis in patients with angina pectoris and hyperthyroidism is very poor in those instances in which the hyperthyroidism is not controlled, both because of visceral degeneration resulting from long-continued hyperthyroidism and because of the constant increase in work thrown on the already injured heart by the hyperthyroidism.

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INJURIES OF THE SPINAL COLUMN AND SPINAL CORD

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THIS paper is based on the observation of a series of sixty-five patients with injury to the spine, examined at The Mayo Clinic during a period of eight years. We do not intend to give a detailed account of all the clinical features exhibited by these patients, nor are we concerned with the recognition of the syndromes characteristic of lesions at different levels of the spinal cord; these are well known and easy of access in any text-book of surgery. After brief consideration of the pathologic anatomy of such injuries, the method of assessing the amount of nervous injury will be illustrated by describing selected cases.

INCIDENCE

Fourteen of our sixty-five patients were females, and fifty-one were males. The youngest patient was eleven years of age, the oldest sixty-one. If mishaps from automobile accidents are excepted, injuries to the spinal column and spinal cord are pre-eminently accidents of active working life, so that one would expect the majority of the patients to be young adults; this is actually the case. In Figure 201 the unshaded part of the column represents the proportion of cases which result from automobile accidents. The proportion is high in the period from ten to thirty years, and it is a sad reflection that the histories show that many of these accidents might have been avoided.

LEVELS OF INJURIES

The curve showing the number of injuries at the level of each vertebra has the usual two peaks: one is in the region of the fifth and sixth cervical vertebræ, and the other is in the

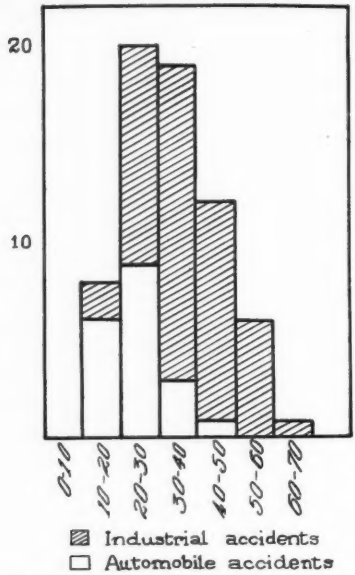

FIG. 201.—The number of spinal accidents occurring in each decade in the present series is shown.

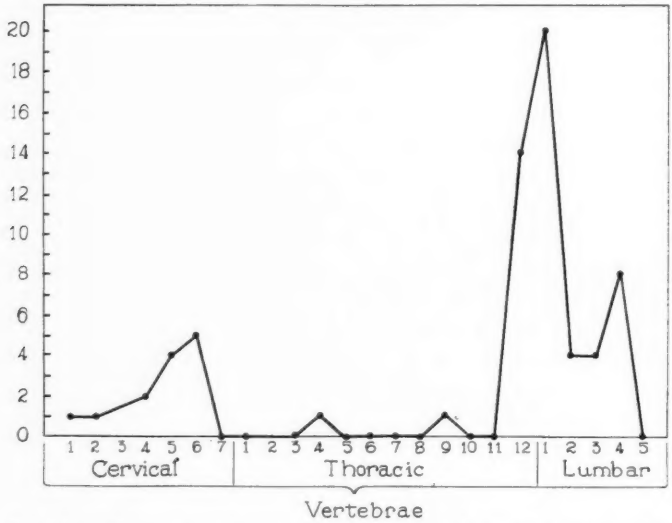

FIG. 202.—The number of cases of spinal injury at the level of each vertebra in the present series is shown.

region of the twelfth thoracic and first lumbar vertebræ (Fig. 202). The curve published by Jefferson,[3] based on 2,006 cases, is similar. The position of the peaks is determined by the juncture, in the lower cervical and thoracicolumbar regions, of relatively mobile, with more fixed, segments of the spinal column.

MECHANISM OF VERTEBRAL INJURIES

Although the majority of severe injuries to the spinal column are the result of indirect violence, direct trauma to the more exposed parts of the vertebræ is not unknown, and in two of our cases was the only factor. One patient who was riding on a box car was struck on the back by a projecting iron pipe, and sustained a fracture of the laminæ of the third lumbar vertebra; the other was tossed in a hay-leader, one of the spikes of which detached, from the body of the ninth thoracic vertebra, a spicule of bone which completely severed the spinal cord. In five cases in which the force was applied close to the site of injury, the typical injury to the vertebral body was complicated by trauma to adjacent parts: to the laminæ twice, to the transverse processes twice, and to the twelfth rib once.

Usually, however, the force is applied at a distance from the vertebra which finally gives way. The mechanics of these injuries has been explained by Jefferson[1, 2] in a series of valuable papers, which we have used freely. Analysis of the factors which lead to injury of the spinal column shows that the most important is "compression between a force above and a resistance below, acting equally in opposite directions." Displacement may result from the combined effect of two additional factors: (1) movement in the joints of the column, usually flexion, and (2) flexion of the column from destruction of its original bony architecture. With regard to the latter, Jefferson has pointed out that the articulated pedicles form a stronger column than do the vertebral bodies, and that the strength of the vertebral bodies is greater dorsally than ventrally.

When a vertebra is compressed it tends to give way anteriorly and to become wedge shaped (Figs. 203 and 204); this

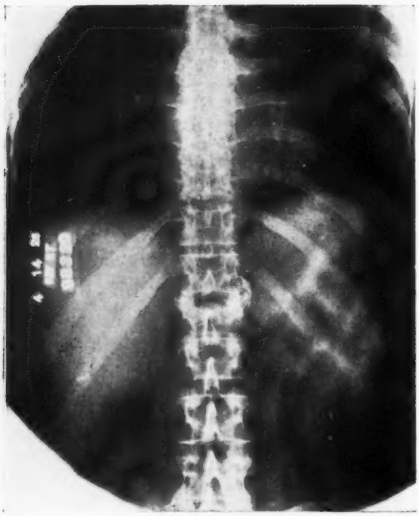

FIG. 203.—Anteroposterior view: Compression fracture of the first lumbar vertebra one year after accident. Attempt at bony repair may be noted.

FIG. 204.—Lateral view: The relative integrity of the posterior part of vertebral body is shown.

at once leads to flexion of the spine, or adds to any flexion already present. This mechanism explains the displacement seen in the common vertebral fracture or fracture-dislocation; for example, that of the first lumbar vertebra, in which the upper fragment passes ventrally, whether the force has been applied cephalad to the lesion (as in falls of rock on the shoulders) or caudad (as in a fall of a person from a height, the person landing in a sitting posture).

FIG. 205.—Fracture-dislocation of the fifth and sixth cervical vertebræ with lateral displacement.

When the atlas is fractured, the line of separation of the fragments usually passes through one or both sides of the posterior arch, where it is weakened by grooves for the vertebral arteries. This type of fracture results from a force which, although insufficient to injure the skull, squeezes the lateral masses of the atlas between the condyles of the occipital bone and the articular processes of the axis. Jefferson's diagram shows that widening of the ring of the atlas must result and this widening

may exceed the limits of bony cohesion. In such cases the head does not move forward or backward; should this factor of forward or backward movement be added, as may happen if the injuring force is a moving one, the odontoid process is likely to be pulled from the axis by the occipito-odontoid ligaments.

In other cases the displacement of the vertebral fragments may not be so typical. Thus, in four of our cases there was posterior displacement; in one case of the sixth cervical vertebra, in one of the twelfth thoracic, and in two cases of the first

FIG. 206.—Fracture of the fourth lumbar vertebra with lateral displacement.

lumbar. In three cases there was lateral displacement—of the fifth cervical, twelfth thoracic, and fourth lumbar vertebræ, respectively (Figs. 205 and 206). In only one of these cases, that of lateral displacement at the level of the fourth lumbar vertebra, was there any relation between the direction of the injuring force and the position finally taken up by the fragments; in this case a tree fell on one of the patient's shoulders, and bent him laterally.

If we exclude from the entire series of sixty-five cases the one case of fracture of the atlas, the one case of fracture of the odontoid process, and the two cases of direct violence, in sixty of the remaining sixty-one cases the injuring force caused flexion of the spinal column. In the one remaining case the vertebral column was forcibly hyperextended by a fall of frozen earth. The injury which resulted was a fracture-dislocation of the fourth lumbar vertebra, in which the fragments showed the common displacement. In the remaining sixty cases the usual great variety of injuring forces was encountered, two of which were curious enough to be mentioned. In the first, an unusually violent "bump" on the saddle while the patient was learning to ride resulted in a compression fracture of the fourth lumbar vertebra. The second patient received a violent blow in the lumbar region from a large rock; he remained erect, and began to run from the scene of the accident. After a few steps he fell to the ground. The roentgenograms gave evidence of a fracture-dislocation of the fourth lumbar vertebra on the fifth; neurologic examination disclosed palsy of the legs, graded 2; with loss of sensation which was complete over the thighs and partial over the legs, and complete paralysis of both vesical and rectal sphincters. The final bony displacement must have occurred after the patient began to run.

PATHOLOGIC ANATOMY

In a large proportion of cases the anterior displacement of the upper part of the bony column leads to obvious deformity, for in these circumstances the spinous process and even the laminæ of the vertebra below the fracture form a projection beneath the skin. On the other hand, a vertebra may be severely injured although external signs are absent; in these cases there is little, if any, immediate displacement or alteration in the vertebral outline. Indeed, it is an open question whether the pronounced deformities revealed by roentgenograms in certain late cases of vertebral injury have been present since the accident, or whether they are secondary to the muscular and ligamentous injury which inevitably accompanies severe injury

to the spinal column. If deformity is present, and an attempt to reduce it is justifiable, the maneuver may be uncommonly difficult to carry out. Locking of articular processes in the new position and entangling of ligaments and intervertebral disks between the fragments are the obstacles to successful replacement of the bones.

Many cases of vertebral injury are easily demonstrated by roentgenograms. On the other hand, there is a group of cases in which detection of the lesions requires not only the most perfect pictures obtainable, but also detailed examination of these by some one who has had much experience in these cases. Good roentgenograms in at least three planes are necessary: anteroposterior, right lateral, and left lateral. Often a lateral view of the spinal column will reveal "wedging" of a vertebra which looks uninjured in an anteroposterior view, and it has been pointed out by Wakeley that a fissured fracture may be invisible in a lateral view taken from one side, yet demonstrable in a lateral view taken from the other side.

The appearance of the injured structures, at necropsy or at operation, naturally varies with the severity of the original injury and with the age of the lesion. The dura is usually intact unless it has been torn by bony fragments detached, for example, from the laminæ. There may be a variable amount of gross destruction of tissue of the cord, with hemorrhages above and below the level of the injury (Figs. 207 and 208). On the other hand, when the pia mater remains intact, there may be no macroscopic evidence of physiologic division. Such a cord is usually much swollen, and on account of the intact and unyielding pia mater this edematous part often occupies a considerable vertical extent. If the pia mater is incised a considerable time after such an injury, the enclosed nervous tissue will be found to extrude as a degenerated pulpy mass. In the course of time the dura mater becomes very adherent to the bony canal. If the injury involves the cauda equina, the nerve roots may be torn from the conus. Fine adhesions also develop between the cord or cauda equina and its coverings, and by compressing the nerve tissue or causing the cerebrospinal fluid to

FIG. 207.—Complete severance of cord as result of fracture-dislocation at the level of the fifth and sixth cervical vertebræ.

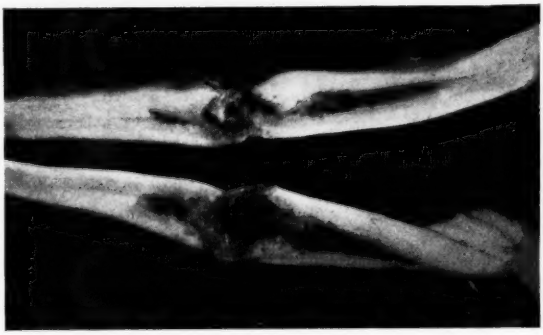

FIG. 208.—Complete physiologic interruption of cord in upper cervical region. The cone-shaped hemorrhagic areas extending upward and downward from site of the original injury may be noted.

be held in loculi may retard or stop progress toward improvement or even cause clinical retrogression. In late cases the injured segment may be replaced by a fibrous strand.

THE NEUROLOGIC ASPECTS OF FRACTURE OF THE SPINAL COLUMN

The spinal column may be fractured without the production of any neurologic symptoms or signs. Occasionally the roots emerging at the site of the fracture bear the full brunt of the trauma to the nervous system; at times the patient experiences the sensation of an electric current coursing through the body below the level of injury without objective evidence of involvement of the spinal cord. Unfortunately, injury to the cord occurs in about a third of cases of fracture of the spinal column and is the gravest of the neurologic complications.

The presentation of a case will bring out the salient features of injury to the cord caused by fracture of the spinal column. We hope the reader will forgive the somewhat pedagogic style of presenting these cases; it is done so for the sake of clarity and brevity.

Case I.—A laborer aged fifty-nine years was engaged in moving a small building across a stream. The bridge, overloaded, collapsed and before the patient was aware of what had occurred he was struck on the head by a timber. He did not lose consciousness but lay helpless in the stream. While he was being carried to a hospital, he observed that all four extremities were completely paralyzed and that he had no sensation below the neck. After an interval of four and a half hours he could move the arms slightly. It was necessary to empty the bladder by catheter and there was fecal incontinence. After four days he could move the left leg feebly. A decubitus, 3.75 cm. in diameter, rapidly developed over the right buttock.

Four days after the injury, neurologic examination showed almost complete paralysis of both arms and of the right leg; the left leg was moderately weak, more so in movements of the hip than of the foot. The intercostal muscles were paralyzed and respiration was diaphragmatic. The patient was able to oppose resistance with the muscles of the shoulder girdle, the biceps, and the brachioradialis muscles; these muscles are supplied largely by segments of the cord lying above the seventh cervical vertebra. The triceps muscles, the muscles of the hands, the trunk, and the legs were involved in the paralysis; they are subservient to segments of the cord lying below the sixth cervical vertebra.

This gives rather accurate information concerning the level of the injury. The lesion to the cord must have been at about the seventh segment, which at this level lies almost opposite the body of the sixth cervical vertebra. The lateral pyramidal tracts, which carry motor impulses downward, are partially protected by the dorsal spinocerebellar tracts at this level. The fibers supplying the left leg must have escaped complete injury. It would be difficult to state how much of the paralysis of the arms was due to trauma to the cells of the anterior horn and adjacent structures of the cord, and how much, if any, was due to injury of the nerves at the intervertebral foramina. This differentiation becomes more important in fractures at the lumbar level, where the segments of the cord lie so much higher than the corresponding vertebral bodies below which the related roots emerge.

The reflexes of the biceps and supinator muscles were normal; those of the triceps muscles were absent. The left patellar and Achilles' tendon reflexes were normal; those on the right were absent. The abdominal reflexes and the plantar responses were absent.

Here again are aids to localization. A tendon reflex is dependent, among other things, on an intact reflex arc. The biceps and supinator muscles were not paralyzed and their reflexes remained normal, since the segments supplying these lay above the level of injury. The triceps reflexes, subservient to the sixth to eighth cervical segments, were absent; presumably this arc was interrupted and therefore these reflexes were abolished. There is good evidence, as shown by Sherrington, that the pyramidal tracts carry inhibitory impulses as well as excitor impulses; accordingly one would expect, and usually finds, hyperactivity of tendon reflexes below the level of injury to the pyramidal tracts. Their absence in this case introduces another phenomenon observed in injuries to the central nervous system; this is the condition called shock, or diaschisis.

In diaschisis, a condition described in detail by von Monakow, recently injured neurones and those in close physiologic contact with them temporarily cease to function. After a period of

time, which may extend four or five weeks, recovery from shock takes place, as was observed in this case. Examination five weeks later showed that the right patellar and Achilles' tendon reflexes had become more active than the left, which had remained normal. Evidently the left pyramidal tract had not been injured sufficiently to bring about such a disturbance. Persistent absence of tendon reflexes below the level of injury was said by Bastian to occur after complete division of the cord. Observation of cases of injuries in war showed that the tendon reflexes reappeared about three weeks after the injury, provided there had been no gross injury to the lower end of the cord.

The abdominal reflexes are dependent on an arc which passes not only through the cord but also through the brain; they are cerebrospinal in function and are sensitive to injury to the pyramidal tracts. Injury to these tracts may explain their absence here; it must also be borne in mind that our patient was fifty-nine years of age and arteriosclerotic; other degenerative changes may have abolished these reflexes before the injury had taken place. With injury to the pyramidal tract one ordinarily expects to find Babinski's reflex positive. Absence of response of the great toe on plantar stimulation is frequently observed with injuries to the cord. In this case they were still absent three months after the injury.

Sensory examination disclosed almost complete loss of sensibility to pain and temperature, with a narrow zone of transition to normal at the upper level, below a plane passing through the second rib anteriorly and the third dorsal spine posteriorly, and moderate loss of these qualities of sensation over the inner aspects of the arms and forearms. The perineal area showed slight loss of these qualities of sensation on the left and almost intact sensibility on the right. Tactile sensibility was impaired to a less degree over the same area. Vibratory sensibility was absent below the injury; joint sensibility was slightly impaired in the toes of the right foot and muscle tenderness was normal.

The sensory changes noted here might serve as the subject of extended dissertation, but we shall consider only some of the more practical points. Sufficiently clear knowledge of the segmental distribution of sensation may be had by consulting any

standard text-book of anatomy. It will be noted that the posterior level passed through the third thoracic spine. At this level the discrepancy between the level of a segment of the cord and the corresponding vertebra is not great; however, when the injury involves the lumbar or sacral segments of the cord, the area of impaired sensation may lie as much as seven vertebral bodies below the level of injury to the cord. We have seen cases in which no external deformity marked the site of the fracture and in which exploration evidently had been determined by the level of the anesthesia without due regard to this difference in levels; consequently the operation had been performed too low. It must also be borne in mind that the cord may be injured by percussion, spreading hemorrhages, and so forth, at distant levels.

The impairment of sensibilities to pain and temperature, without a corresponding degree of involvement of tactile sensation, at once suggested two possibilities. One was that a pencil-shaped hemorrhage (Fig. 208) had extended along the region of the central canal, from the cervical to midsacral levels, and had blocked the fibers which carried the impulses of pain and temperature as they crossed anterior to the canal, similar to the disturbance often observed in syringomyelia. The other possibility was that the trauma in the cervical region had blocked the more superficially lying lateral spinothalamic tracts which carry these qualities of sensation. The latter is usually the case. The predominance of involvement of the right pyramidal tract, associated with the greater impairment of pain and temperature sensibilities on the left, as found in subsequent examination, thus constituting a partial Brown-Séquard syndrome, and the rapid recovery of sensation, as we shall see later, justified the assumption that the injury in the cervical region rather than a pencil-shaped hemorrhage in the central canal had been responsible for the impairment of pain and temperature sensibilities.

A further point of interest lies in the relative preservation of sensation in the vicinity of the perineum. Kerppola showed in his study of tumors of the cord that this condition is more common in compression of the cord from the outside than in destruc-

tion of the cord by some intrinsic lesion. We have found this to be one of the most reliable criteria in distinguishing between extramedullary and intramedullary lesions. Its presence carries with it the suggestion of a relatively better prognosis.

Tactile sensibility is often less involved, as it was in this case, when the cord is injured asymmetrically, since these impulses ascend both in the opposite anterior spinothalamic tract and in the homolateral posterior column; the discriminating modalities of tactile sensibility, such as directional stimulation, simultaneous two-point recognition, and localization, ascend in the posterior columns.

Vibratory sensibility, which is transmitted upward through the homolateral posterior column, is more sensitive to injury than some of the other forms of sensation. It is frequently impaired in arteriosclerosis and, as a rule, more so in cases with hypotension than in cases with hypertension. Although our patient had arteriosclerosis, with evidences of hypertension, the injury, rather than some other disease of the cord, was evidently responsible for the loss of vibratory sensibility, since it had returned to almost normal when the patient was last observed. Joint sensibility, like vibratory sensibility, ascends in the homolateral posterior column, but is more resistant to injury. The predominance of injury to the right side of the cord would explain the slight impairment noted in the right toes. Muscle tenderness is usually less impaired than other forms of sensation, as it was in this case. In tabes, however, its loss in the presence of otherwise relatively intact sensibility at once carries with it the suggestion of syphilis.

The roentgenogram of the cervical portion of the spinal column showed a fracture with forward dislocation of the sixth vertebra. The spinal fluid was clear, under a pressure of 20 cm., measured in water, and responded promptly to compression of the jugular veins. The patient experienced a good deal of difficulty in respiration and occasionally became cyanosed. A plaster bandage extending from the thorax well up under the chin and occiput was applied; subsequent roentgenograms showed that the body of the sixth cervical vertebra was in satisfactory alignment.

September 24, thirty-nine days after the first examination, a moderate degree of power had returned to the right leg. Power in the left leg and both

arms remained about the same, but slight atrophy had developed in the paralyzed muscles of the arms. Reflexes of the triceps muscles remained absent. The digital reflex (Hoffmann's sign), which is elicited by sudden extension of the terminal phalanx of the first or second digit when the hand is in a position of relaxation and which consists in a flexor response of the terminal phalanx of the thumb, was strongly positive on both sides; this indicated involvement of the pyramidal tracts above, although a moderate response may be present normally. The right patellar and Achilles' tendon reflexes had not only returned but were more active than those on the left. Sensation had improved remarkably; there was only slight impairment of tactile and pain sensibilities over the median aspects of the forearms and very slight impairment of pain and temperature sensibilities over the left half of the body below the second rib. Thus, the Brown-Séquard syndrome, obscured by the initial findings, came into greater prominence as the patient improved, and indicated that the lesion was more severe on the right side of the cord.

The patient had urinary retention for four weeks after the accident, following which the bladder emptied automatically at intervals. Control of the bowel remained impaired.

Six months after the patient had left the hospital, a letter from his physician stated that the patient could sit up without support, that power of the legs had improved, that the left arm, but not the right, could be moved well, that the bladder, but not the rectum, was under normal control and that the pressure sores had healed.

Since the lower end of the cord is surrounded by an increasing number of nerve roots and the cord in adults ends opposite the interval between the first and second lumbar vertebræ, injuries at this level present somewhat more complex data. In the following case there was a fracture-dislocation of the fourth lumbar vertebra.

Case II.—A clerk aged thirty-six years was injured in March, 1921, by the turning over of his car. At once he lost sensation and power of motion in the lower extremities. The bladder had to be emptied by catheter for three months, and the bowels moved only with the aid of enemas. A decubitus appeared over the sacrum.

Eight months after the injury neurologic examination disclosed some weakness of the muscles of the thighs, almost complete paralysis of the hamstring muscles, and abolition of all movements below the knees. The paralyzed muscles were extremely atrophic. The reflexes of the patellar tendons were difficult to elicit, and those of the Achilles' tendons, the bulbocavernosus

muscles, and the anus were absent. Sensation was impaired (Fig. 209) A roentgenogram of the spinal column showed a fracture and forward displacement of the fourth lumbar vertebra.

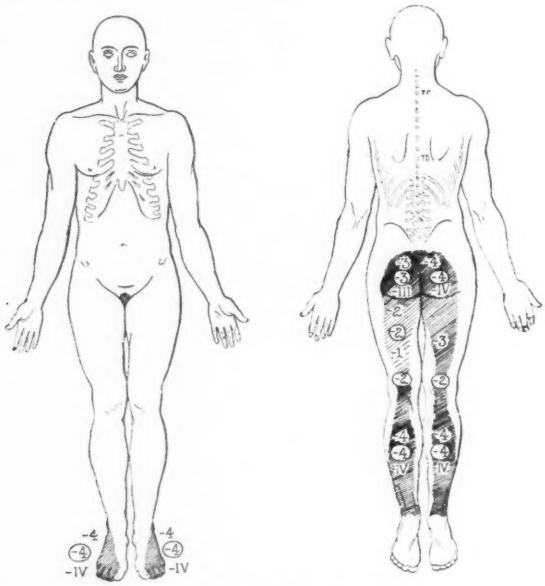

FIG. 209.—Sensory disturbance in a case of fracture-dislocation of the fourth lumbar vertebra.

Laminectomy disclosed that the posterior arch of the fourth lumbar vertebra had been crushed into the canal; this resulted in compression of the nerve roots.

The initial weakness of the thighs was probably the result of indirect trauma, possibly hemorrhage. The clinical picture noted could be explained readily by the severe injury to all roots passing the fourth lumbar vertebra, as observed at operation. In the following case the fracture was at a higher level, the second lumbar vertebra, but the segmental disability was lower.

Case III.—A farmer aged fifty-six years had dropped thirty feet into a well, landing on the buttocks. Neurologic examination revealed an area of

anesthesia, including the perineum, and extending midway over the buttocks. Sphincteric control and sexual power were lost (Fig. 210).

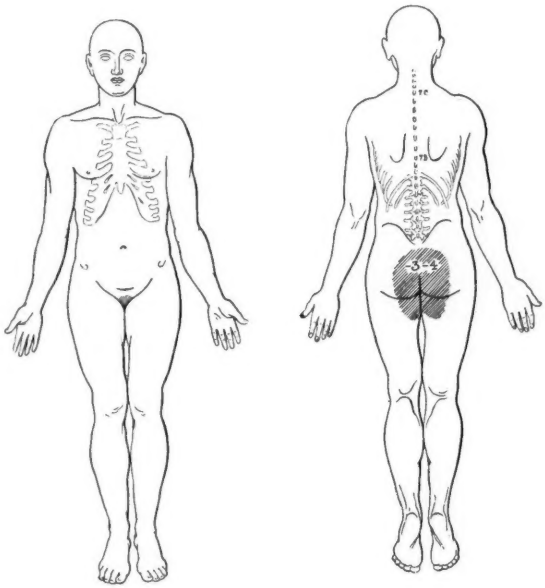

FIG. 210.—Sensory disturbance in a case of fracture of the second lumbar vertebra with injury to the conus.

Evidently the injury in this case was to the more friable conus, whereas the surrounding elements of the cauda were sufficiently tough to withstand the injury.

Sphincteric, vasomotor, pilomotor, and secretory disturbances frequently follow injuries and are variable in their manifestations. In severe injuries to the cord these functions are often interfered with to a degree that is governed by the level of the lesion, but which does not necessarily coincide with the somatic level.

The sphincters are usually in a state of contraction for a variable length of time following injury to the cord. At the onset catheterization is often necessary and enemas may be required to empty the bowels. Subsequently the sphincters

may relax and remain so, or a state of automatic reflexia may ensue.

We observed a patient who had complained bitterly of root pain, for the relief of which a hot-water bottle had been applied to the painful area. Later the outline of the water bottle was clearly indicated by a burn, with hyperemia and blistering of the skin where it had been in contact with the anesthetic area, but there was no trace of such reaction above this level where sensation was normal. Whether this can be explained only by assuming that some trophic disturbance existed is open to question.

With cervical lesions persistent priapism is not uncommon. Explanations have been offered but the cause remains unknown. Interesting dissociation of sexual functions may be observed in injuries to the sacral part of the cord. Thus, one patient, although anesthetic, could produce erection, but ejaculation occurred only once. The same condition, but without anesthesia, existed in another patient after the removal of an intramedullary tumor from the lower end of the cord.

Conception and normal but painless parturition occurred in one of our patients who for years had been anesthetic below the thorax as the result of a fracture of the spinal column.

Cases are occasionally observed in which paraplegia develops slowly following injury to the spinal column with or without involvement of the cord at the time of injury. The time of appearance of the subsequent paraplegia is variable. Usually the disturbance in sensation and in motility is fairly symmetric and all qualities of sensation are equally involved, often without a sharp line of demarcation at the upper border of the disturbed area. This delayed paralysis may be due to meningomyelitis, to spinal gliosis, or to circumscribed cystic meningitis. The prognosis in these cases is uncertain, even with operation.

TREATMENT

Injury to the spinal column which results from indirect violence is never an urgent surgical condition. There are several reasons why this should be so. First, any injury to the cord is immediate

and irreparable; if the injury is in the region of the cauda equina, it is technically impossible to repair the nerve roots; and even if this were possible, only the anterior roots would resume their function. Second, both extradural and intradural extramedullary hemorrhage are extremely rare as causes of compression of the cord; nor do indriven fragments of bone cause increasing symptoms, for they do not grow larger. Third, no final estimate of the amount of injury to nervous tissue can be made until the stage of spinal shock has passed; this may last from a few days to three weeks. And finally, operations undertaken during the stage of spinal shock are attended by high mortality. After the period of spinal shock, neurologic evidence of complete interruption of the cord is an absolute contraindication to operation. If some conductivity remains in the cord, and if there is reason to suppose that the lumen of the bony canal has been reduced by the fragments, exploration is justifiable at this stage. As a test of reduction of the size of the lumen of the bony canal, Queckenstedt's maneuver is valuable. Indeed this is of value at all later stages, for if recovery has reached a certain stage, and has then stopped, the test will show if there is spinal subarachnoid block, possibly the result of membranous adhesions (meningitis serosa circumscripta). This condition may be treated by performing laminectomy, and carefully separating the adhesions; in such cases it is best to leave the dura mater open, and to rely on accurate closure of the muscles to prevent leakage of cerebrospinal fluid. In the region of the cauda equina operative interference aims at disentangling matted nerve roots so far as is possible, and in dividing any band of fibrous tissue which may be compressing them. At all levels, operations for vertebral injuries may be very difficult. The displacement of fragments alters the relation of the bony canal to the surface, and may reduce it, in part of its extent, to a narrow, twisting passage. In order to avoid accidental injury to nervous tissue, it is wise to work from the known to the unknown, and to identify the structures above and below the lesion before trying to rectify it.

With the exception of such cases as have been mentioned

here, the only procedure which is justifiable in cases of spinal injury is an attempt at closed reduction. We say attempt advisedly, because the interlocking of articular processes and jamming of torn intervertebral disks may be enough to prevent replacement; in fact, replacement is regularly easy only in hopeless cases, in which the amount of injury has been great and the cord is completely interrupted. But in the cervical region this bony interlocking may be a life-saving matter for the patient. The cervical canal is roomy, and it is not uncommon to see patients who have sustained a fracture-dislocation in the middle cervical region show few, if any, signs of injury to nervous tissue. In these cases the cord has been saved from destruction by the inferior articular processes of the dislocated vertebra catching on the high posterior lip of the vertebral body below it. If the injuring force is not too great, this contact is sufficient to prevent further displacement. Whether the fragments have been reduced or not, a prolonged period of rest is necessary.

It is possible that the effects of the pressure of the edematous fluid which distorts the cord if the pia mater is intact might be limited by the use of hypertonic solutions, as is practiced after injuries to the brain. An early course of treatment by roentgen ray is also worth considering in cases of incomplete division of the cord, as tending to limit secondary gliosis.

Since the severity of the inevitable urinary infection is by far the most significant single factor in prognosis, any method of deferring and diminishing this must be actively pursued. When the lesion has led to complete paralysis of the bladder, it may be advisable to perform suprapubic cystostomy immediately. It is much easier to wash out the bladder by this channel, and also the irritant effect of an indwelling catheter on the sensitive mucous membrane of the urethra is avoided. The cystostomy does not cause inconvenience to the patient and may be allowed to function even after automatic micturition is established.

When the patient is not seen by the surgeon until the clinical features of the case are stable, two problems may be presented. In any case, even when the cord is completely interrupted, there

may be complaint of root pains at or just above the level of the lesion. In our experience these pains tend to become less severe, but it may be necessary to perform rhizotomy or cordotomy for their relief; of the two operations, we prefer the latter.

A problem is presented by those patients who have recovered a certain amount of spinal function, and who wish to be independent of a wheelchair. They are to be dealt with mainly by the orthopedic surgeon, but when the bar to walking is an unduly spastic condition of the lower extremities, neurosurgical procedures also are applicable. Carefully planned operations of the Stoffel type will diminish the stiffness of the muscles; but the surgeon must be careful to strike a mean between sufficient reduction of spasticity, and conservation of as much motor power as is possible. The results from neurectomy of both obturator nerves are especially gratifying; we have been impressed by the fact that after this operation the legs, as a whole, become much more manageable, although only the adductor group of muscles has been deprived of its nerve supply.

Unfortunately many of the patients with injury of the cord are left with a severe and permanent disability. Some have lost not only the means of earning a livelihood, but have also been bereft of their usual pleasures. One of the few benefits of the war was the widespread institution of selected occupation as a therapeutic measure. This was not a new idea, but it had been left to a scattered few endowed with rare intelligence and a fine sense of compassion for their suffering fellowmen.

The same problem confronts us here. An honest effort must be made to make the lives of these patients more easily bearable, to instruct them in some useful occupation so that they may be brought to realize that they still have obligations, and to impress on them that the most useful functions of the body and of the mind have been preserved. By heroic example they may exercise a powerful influence for good. Thoughtful relatives, too, will coöperate and make the patient feel that he is indispensable to the welfare of the family.

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EPIDEMIC ENCEPHALITIS: RESPIRATORY SYNDROME

HARRY L. PARKER

IN 1921 I reported a small series of cases of encephalitis and associated disturbance of respiratory function. They have shared in the general tendency toward chronicity in epidemic encephalitis, and in the eight years that have passed the following up of these patients and the accumulation of new material have been of sustained interest.

Although many variations occur in respiratory disturbances in epidemic encephalitis, there is sufficient similarity between some of them to permit of the disturbances being classified in three main groups. The first group is that in which there is a disturbance of rate and depth of respiration or simple hyperpnea; the second group is considerably more complex and includes disturbances of respiratory rhythm with many bizarre clinical features associated with them; the third group is even more varied and complex, and consists of various tics and mannerisms affecting the function of respiration more or less as a whole. One of these divisions may merge into the other, and in any one case all three may be combined. The classification nevertheless serves a useful purpose if only to demonstrate an ascending degree of complexity of functional disturbance.

SIMPLE HYPERPNEA, DISTURBANCE OF BEHAVIOR, EXAGGERATED MOTOR ACTIVITY AND PARKINSONIAN SYNDROME OF SLIGHT DEGREE

Case I.—A boy aged fourteen years was brought to The Mayo Clinic September 20, 1929, because of restlessness and respiratory disturbance. In November, 1919, rather suddenly, marked motor activity, restlessness, and insomnia had developed. This had continued without remission for six weeks, during which time he constantly had moved around, whistled and sung, and had kept up a continuous chatter. He had picked his bed clothes to pieces and it had been scarcely possible to keep him in bed. During this time he had

run a continuous temperature of about 103° F. The insomnia gradually had improved but motor restlessness, with periods of utter exhaustion, had continued. He had returned to school for a short time but had been unable to sit still in classroom and had disturbed all other pupils by his restlessness and pranks. He had been unable to play with other children because of extreme lack of concentration, a tendency to interfere with others, and outbursts of violent temper which caused him to assault his playmates. In 1923 attacks of rapid, puffing respiration had been noticed and these had continued up to the time when he was brought to the clinic. They had been brought on especially by excitement and emotional stimuli, but even when the patient was quietly reading a book he would suddenly start breathing at a rapid rate and would continue to do so for nearly an hour. As years went on there was gradual and steady improvement in his restlessness, insomnia, and breathing, but still these symptoms remained marked enough to make his case a distinct problem.

The patient was somewhat undernourished, rather restless, and talkative, but on the whole likeable. He had a definite parkinsonian syndrome, characterized by mask-like expression, slow, stiff movements, and lack of swing to the arms when walking. He held his mouth open, and at irregular periods breathed rapidly and noiselessly, for no particular reason. These periods of hyperpnea lasted, on the average, ten to twenty minutes, were particularly marked when he was under examination and excited, and less evident when he was left alone.

The essential value of this report is to show the long-drawn-out course of the disease. For years the patient's parents have been hoping for recovery. The boy has grown and developed apparently normally, but all of the original complaints have persisted in a milder form. Altogether, the history is a fairly typical one and what the ultimate outcome may be is absolutely unknown. Disturbances of control in the rate and depth of respiration have remained more or less permanent in this case, as well as in Case II, in which they constitute a more prominent portion of the disease as a whole.

SIMPLE HYPERPNEA EXAGGERATED BY EMOTION MORE OR LESS CONSTANTLY PRESENT AND INTERFERING WITH OCCUPATION, MILD BEHAVIOR DISTURBANCE, AND INSOMNIA

Case II.—A girl aged thirteen years was brought to The Mayo Clinic February 21, 1922, because of rapid breathing and sleeplessness. The child had been apparently well up to two and a half weeks previously, when she suddenly had complained of a sense of suffocation and had insisted on going outside into the open air. Respirations had become rapid and she had complained of tingling in the hands and feet. The same night she had slept

scarcely at all, was on her feet panting for breath, and this condition had continued day and night up to the date of her admission to the clinic. During rare periods of sleep breathing had been normal, but following a sigh she had been accustomed to awake in terror, complaining of suffocation, and to leave her bed to pant and puff, and to obtain no more sleep for the rest of the night.

The patient was well nourished. Respiration was rhythmic and without noise, but extremely rapid, varying between 50 and 60 a minute. The respiratory rate was not materially influenced by physical exertion such as hopping, climbing stairs, or running. The sense of suffocation and the respiratory rate were increased when she lay on her back. Movement of the abdomen during respiration was exaggerated. When the examiner placed one hand on the thorax and the other on the abdomen they see-sawed up and down in a remarkable fashion. Under emotional stresses the respiratory rate was considerably increased.

The patient's sleeplessness and respiratory difficulty continued for three weeks; then her tonsils were removed. The hyperpnea became somewhat lessened, but insomnia by night and restlessness by day continued. She had to leave school because of this restlessness and inability to sit still. She was unable to recite in class, for being required to do so brought on paroxysms of rapid breathing. A year after the first admission the same rapid breathing, sighing respirations, restlessness, and emotional instability were present. The trouble in breathing and sense of suffocation had now become intermittent rather than constant, and she was sleeping somewhat better at night. Advice was given to continue her education at home and a plan was drawn up for work and rest.

The patient was lost sight of for several years, but in 1926 she appeared again, with precisely the same complaints of nervousness, restlessness, insomnia, and rapid respiration; the last exceeded all bounds when she was under any emotional strain. As before, all ordinary means of treatment, including hydrotherapy, hypnotics, and sedatives, failed entirely. In spite of the inability of my colleagues and me to benefit her the patient has continued to consult us at intervals of every few months up to the present month (September, 1929). She has developed normally and has become an attractive, rather pretty, girl. Always, however, she has presented the same breathless, restless, excitable appearance, and continuously has complained of inability to get her breath and to concentrate on whatever she may be doing. She has tried various types of employment but has failed each time because, when pushed for time, her breathing has become uncontrollable and the intense desire to get into the open air has got the better of her. In 1928 she married a boy of her own age, on the spur of the moment, and marital relationships from the first have been unsatisfactory. She became pregnant in 1929 but miscarried at the sixth month and the baby lived only a few hours. When last seen she had more or less settled down to her lot in life but complained just as vigorously as ever of precisely the same complaints that had begun so mysteriously seven years before and had persisted so consistently.

In the beginning there might have been some possibility that

the patient was a constitutionally psychoneurotic child with hysteric manifestations in the form of hyperpnea. The family, however, had been uniformly stable, as was the patient, as far as the history goes, up to the onset of her illness. As time went along, the persistence of the complaints and the complete lack of association with the varying environment led me to seek an explanation in some more recently acquired type of pathologic process. The story has been consistent in the extreme, and although minor details have influenced the affliction temporarily, on the whole it has remained distressingly permanent. Furthermore, the close resemblance of the respiratory disturbance to that in Case I and to many other cases wherein the diagnosis of epidemic encephalitis was certain, both because of the manner of onset and the course, leaves little room for doubt as to its origin and nature. As will be seen later in this paper, the age of onset and the behavior reactions of the patient represent another important point in the diagnosis.

Cases of simple hyperpnea, if not accompanied by other manifestations of encephalitis, are extremely chronic. Nevertheless, they present, on the whole, a better prognosis than the more complex types of respiratory disturbance. Possibly the latter represent a more severe type of the disease with more widespread and profound structural injury to the brain. Usually they are accompanied by other clinical evidence of severe involvement. From the standpoint of care, these more severe cases are a very different and extremely more distressing problem. They tax the resources of the physician and the relatives to the utmost, and at the same time they represent the most dramatic and striking types of respiratory disturbance in epidemic encephalitis.

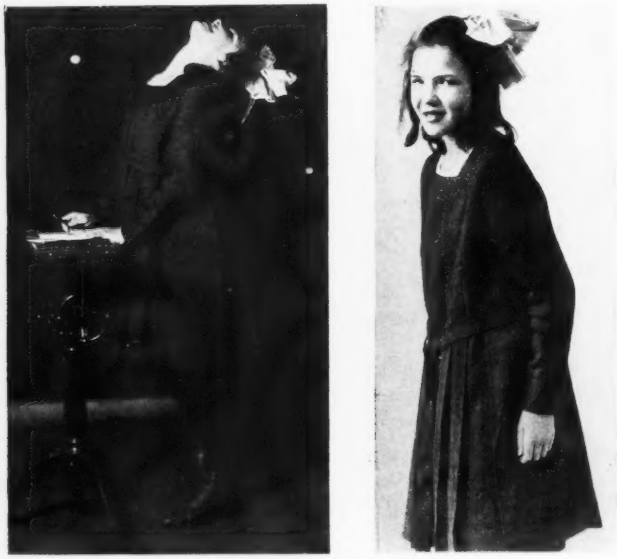
SEVERE RESPIRATORY DISTURBANCES COMPLICATED BY MANY OTHER MANIFESTATIONS OF ENCEPHALITIS

Case III.—A girl aged twelve years was brought to The Mayo Clinic January 20, 1922, because of attacks of irregular breathing. The child had been perfectly well up to March, 1920 when she had contracted influenza. This had been characterized by headache, malaise, and fever which had lasted about four days. The other members of the family had been affected

and the attack had not seemed to differ materially from those of the others. She had recovered and had returned to school about ten days after the illness. It then had been noticed that her hands, trunk, and legs moved in irregular, jerky choreiform fashion. Her sleep had become poor. She would leave her bed, and her mother had found her, many a night, working in her night-gown over some lesson. She had slept only two to three hours at night and often had gone for twenty-four hours without sleep. Her school work had become poor, and she had done badly at school in spite of tremendous application to her work. A month after the attack of influenza she had had double vision for a day. The choreiform movements and insomnia had lasted twelve months and then gradually had diminished, but a breathing disturbance had appeared. This, at first, had been merely an increase in speed and depth of respiration with but little irregularity in rhythm. Later, the respiratory sounds had become noisy, and about eighteen months from the onset of the trouble the complex syndrome of breathing had developed which had led to her being brought to the clinic. These attacks had become more and more frequent and at first had appeared only in the daytime. Later they had begun to appear also at night. She had lost consciousness in some of the attacks and on one occasion she had fallen on a chair and had broken it. Her personality had changed; she had become emotionally unstable, impulsive, disobedient, passionate, and stubborn to an extreme degree. Her ability to do her school work had diminished greatly and she had seemed somewhat mentally deteriorated. Attempts had been made to break her of her attacks of difficult breathing and she even had been beaten during one of them. Nevertheless, both verbal and physical punishment had seemed to make her repeat her attacks more frequently and to make her more stupid, nervous, and emotional.

The patient was well nourished. A certain degree of mask-like expression, rounded shoulders, a slow gait and awkward, clumsy movements were noted. The parkinsonian syndrome was, however, mild at this time. The patient's speech was jerky and quick, and she could not carry on a conversation with any logical sequence because of frequent change in lines of thought. Her intelligence seemed to be fairly well preserved between the attacks, but it was obviously dulled during a succession of them. She had the characteristic breathless expression with half-open mouth, and on nearly all occasions apart from her attacks she was either breathing noisily, forcibly, and deeply or scarcely at all. In an attack she suddenly jumped up from her seat, sought a hiding place and went through an attack. This began with noisy, rapid respirations, gradually increasing in speed and depth, until suddenly she threw her head back impulsively until the occiput and spine almost met; her head and eyes were slightly turned in the direction of the examiner. There was a half smile on her face and her throat showed itself tense and prominent. The thorax was pushed forward and distended. The back was bent in the lumbar region, the abdomen was thrust out and the arms were at the sides, half flexed at the elbow. The hands were clenched. The feet were together in the position of "attention." While her breath was held, her face, at first red, became cyanosed, and after twenty or thirty seconds she allowed the pent-up air to escape through her clenched teeth

with a hissing noise. Slowly she turned her head and stooped over slightly, hardly breathing for from ten to fifteen seconds. Again a period of noisy hyperpnea and again the impulsive throw back of the head occurred, with a repetition of the whole sequence of actions (Fig. 211). Usually, this paroxysm was repeated two or three times and her expression gradually changed from that of wilful pleasure to a gray, ghastly, dazed look. At the end of a series she would stagger slightly and either fall or drop on a seat, staring straight ahead with the same dazed, fixed expression, ashen or cyanosed



A *B*

FIG. 211.—(Case III.) Epidemic encephalitis; respiratory syndrome; *A*, posture of patient during period of breath-holding; *B*, posture during rest period, ready for another period of hyperpnea that will end in forced holding of breath. Early parkinsonian syndrome.

face and imperceptible breathing. While at this stage, her consciousness was either dulled or actually absent; she could be aroused if a loud command was given, if the fingers were snapped, or if she was shaken. The color would then return, breathing would become almost normal until she would jump, panting noisily, again to seek a hiding place and go through the whole syndrome again.

Ample opportunity to observe the child was afforded, and the attacks persisted without cessation for more than two years. They gradually diminished after that, but her behavior did not improve and she was hard to man-

age. Attacks of conjugate upward spasm of the eyes developed. The eyeballs would rotate upward and stay up for from four to six hours at a time, so that only the sclerotics were visible; the pupils would disappear under the upper lid. During these occasions she had to stop all activities and lie down because of being unable to see. Occasionally the reverse would take place and a downward spasm of the eyes would occur, lasting the same period of time. Gradually, in the following year, she became more quiet, less active, slower in all her bodily movements, and she experienced greater and greater difficulty in dressing herself or in using her fingers for small, complicated movements. This parkinsonian syndrome, that was very slight on the occasion of her visit here, gradually increased and dominated all other

FIG. 212.—(Case III.) Same patient as that shown in Figure 211, five and a half years later; the parkinsonian syndrome was marked but the respiratory symptoms had ceased.

manifestations (Fig. 212). She began to experience considerable difficulty in eating and swallowing and finally became bedfast. In May, 1928, she contracted influenza, later bronchopneumonia, and she died from this complication. The duration, from onset to death, was eight years and two months.

Necropsy was not permitted, but no doubt it would have shown fairly definite and widespread injury to the tissues of the brain. Followed from onset to termination, the course was definitely downhill with new phases of

the disease appearing from time to time. The disease began with choreiform movements and insomnia, respiratory irregularity, and change in behavior. Oculogyric spasms appeared in due course. The parkinsonian syndrome that was in the background at first gradually became more evident, then dominated the clinical picture and ultimately led directly or indirectly to death. This is frequently the case, and although in many patients all other clinical manifestations may come and go, once the parkinsonian features are developed they tend to progress, and they become a serious menace to happiness, to usefulness, and even to existence.

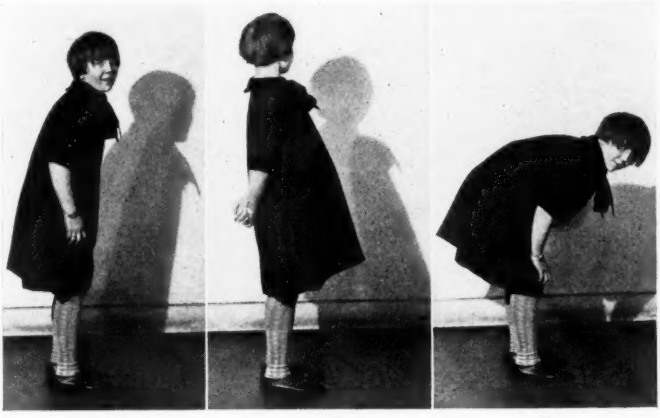
At the present time difficulty would not be found in establishing a diagnosis of encephalitis, but in 1921, because of the patient's emotional reactions, partial voluntary control of the attacks and, above all, their peculiar nature, hysteria was at first considered as a possible diagnosis. It was rejected finally because of the earlier history, the severity of the insomnia and falling attacks, and especially because many more similar cases appeared soon afterward as part of a prevalent epidemic.

HYPERPNEA, BREATH-HOLDING, CONVULSIVE ATTACKS, DISTURBANCE OF BEHAVIOR WITH SLOW IMPROVEMENT TO DATE OF EXAMINATION

Case IV.—A girl aged fourteen years was brought to The Mayo Clinic February 22, 1929, because of respiratory disturbance. She had had influenza in the spring of 1920 but no apparent immediate after-effects had been noticed. In January, 1925 she had become drowsy and dull, had yawned frequently and had complained of rapid exhaustion, but marked somnolence had not been noticed. In March, 1925, her tonsils had been removed, and within a few weeks her breathing had become irregular and periods of voluntary holding of the breath had appeared. These had become increasingly frequent and later almost constant, night and day. She had lost sleep at night because of frequent attacks of hyperpnea and had been accustomed to jump out of bed every few hours to go through a cycle of respiratory disturbance. In September, 1927, epileptiform convulsions had appeared, apparently not associated with respiratory disturbance. In the year previous to her coming to the clinic a change had been noticed in her facial expression, posture, and gait. However, the frequency and severity of respiratory attacks had lessened in the same time and sleep had improved. She had become more irritable and hard to manage.

The patient was obese, with a definite parkinsonian syndrome. Her face was expressionless, her mouth remained open and all her movements were slow. She did not swing her arms when walking but carried them awkwardly and stiffly at her side. There was frequent repetition of the respiratory irregularity which constituted the chief complaint. While sitting quietly, breathing was almost imperceptible, but suddenly she would get up quietly,

breathe noisily, rapidly, and deeply, with increasing speed and depth, until at the height of a deep inspiration she would arch her back, throw her thorax forward, arms akimbo, and hold her breath until cyanosis supervened. With this, her expression became dull, her eyes became fixed, and seemingly when she was on the point of falling unconscious, she would suddenly bend forward, hands on knees, and exhale rapidly, forcibly, and noisily. On completion of this, the cycle would begin again and would be repeated many times. Then, obviously exhausted, she would drop back on the seat looking drowsy, dull, and stupid. Another bout might follow in a few minutes, and so on throughout the twenty-four hours (Fig. 213).



A *B* *C*

FIG. 213.—(Case IV.) Epidemic encephalitis; respiratory syndrome; sequence of events, *A*, marked hyperpnea following a series of attacks with characteristic facial expression; *B*, posture during holding of breath; *C*, posture during phase of expiratory hyperpnea.

This history is recorded because it shows the marked similarity in the general characteristics of this type of respiratory disturbance in epidemic encephalitis. The onset of disturbance in breathing in this case was somewhat later in the history of the epidemic, but when the patient came to the clinic it had been present four years, with no more than slight improvement.

So far (Cases I to IV inclusive) all patients described were children or adolescents at the time of onset of the disease. Actually they represent a far larger number than the adults, as shown in Figure 214. Adults, nevertheless, are not exempt, and one

of the worst cases that I have observed was that of a huge, muscular policeman, aged twenty-five years. The patient was seen in January, 1926 with the same syndrome of hyperpnea, holding of breath, and unconsciousness. The attacks came on rather suddenly while on his beat and lasted without remission day and night for more than two years, when they just as suddenly disappeared. As with many others, his attacks came on when lying down, and for rest he must needs stand or sit. The night was by far the worst time for him and during periods of breath-holding he went into opisthotonos and became sweaty, cyanosed, and rigid. The release of his breath and expiratory respirations were in a thunderous bellow, heard many blocks away. In the case of so large a man the attacks were a shock to both eye and ear. After drifting around from place to place, including a few months at a state hospital for the insane, he returned home and suddenly recovered. When last heard from more than a year ago he was back at work in the police department.

This type of case is perhaps the more common in the whole series, and the same cycle of hyperpnea, holding of breath, cyanosis, unconsciousness, recovery, and hyperpnea recurs with amazing regularity and similarity. Stretching the body and arms, as in the morning yawn, facial grimaces, and contortions and athetoid movements are common accompaniments of the period of breath-holding. Stooping over, bent almost double, seems to be the common position after the period of voluntary apnea is over. The mental reactions of the patients to their disease are curious. Little satisfaction is obtained from questioning them as to why they perform in such a manner. Usually the answer conveys the idea that they are compelled to do so, could stop if they liked, but feel better if they go on breathing, stretching, holding the breath, and the like. Some patients seem to obtain some pleasure from the attack and beg to be left undisturbed, to continue until well-nigh exhausted and half conscious. My patient, who was a policeman, always begged for "just one more," and many of the children sought hiding places, where they went at it with tremendous vigor and determination, but often be-

trayed their presence by the characteristic noisy respirations. Manual assistance in breath-holding was sought by two patients, one by holding the nose and one by throttling himself. Yet, in all senses they seemed unsociable, unhappy unfortunates; one patient committed suicide, another fell against a red-hot stove and burned himself severely. Night is always the worst time, and the patient's relatives, nurses, and physicians are well exhausted after many months of this affliction have passed without sign of amelioration.

Patients with respiratory tics and mannerisms (Cases V and VI) constitute another group, but these symptoms are most frequently associated with some other syndrome of encephalitis, such as the parkinsonian syndrome, insomnia and disturbance of behavior. Rarely do the respiratory tics and mannerisms form prominent symptoms. Among those described elsewhere, and seen at the clinic, are spasmodic cough, hiccoughs, yawning, grunting, sighing, sobbing, and sniffling. The simple hiccough has occurred in epidemic form, but rarely lasts as long as the other abnormalities. The spasmodic, dry, barking, purposeless cough is a more common chronic manifestation. It may be incessantly repeated during the twenty-four hours, and may distress those who are forced to listen to it. Needless to say, physical signs in the thorax or larynx do not accompany it.

PAROXYSMAL COUGH, INSOMNIA, DISTURBANCE OF BEHAVIOR, AND MARKED PSYCHOMOTOR ACTIVITY

Case V.—A boy aged sixteen years was brought to The Mayo Clinic May 15, 1925, because of restlessness and cough. He had had rheumatic fever in 1917 and since then had been supposed to have cardiac disease. In January, 1925, he had had what had been called influenza. This had consisted of prostration, malaise, fever, and headache. He had been in bed only a few days, but extreme lassitude and weakness had followed. Ever after this last illness marked restlessness and irritability had been noticed. He had been constantly on the move, had picked his nails to the quick, had hardly slept at all, and had been a constant care. There had been a change in his behavior, he had become talkative, impatient, impulsive, restless, and untidy, and had lost all interest in his friends, his school work, his appearance, or anything requiring sustained thought. Abusive and extremely irritable, he once had struck his brother with a knife. Salivary flow had increased, and constant spitting had been a disagreeable feature. Two months before

admission constant, rhythmic, purposeless dry cough had appeared, but the most severe feature of the illness had been sleeplessness. He had been awake almost every night and all night, walking around the room, whittling objects with his knife, spitting, constantly barking away with his noisy cough and talking incessantly. He had rattled the windows, paced the floor, and constantly awakened his parents to ask questions. Usually he had slept a few hours in the day, but he had been known to go twenty-four to forty-eight hours without sleep.

The patient was restless, red-eyed, and suffered from paroxysms of rhythmic dry, purposeless cough. He seemed tired and dazed, yet constantly on the move. He was talkative, without sequence of ideas, and it was impossible to obtain a clear, consecutive story from him. He had well marked signs of rheumatic mitral endocarditis. The disease continued unabated for seven months, when he died from exhaustion and cardiac failure.

The spasmodic cough in epidemic encephalitis is more distressing to those around the patient than to him, and never by itself leads to a fatal issue. In the patient whose case has just been reported death undoubtedly resulted from the terrific strain from insomnia and exaggerated motor activity. Frequently, however, a case begins with spasmodic cough, and, as in one case observed at the clinic, goes on to the more severe hyperpnea and apnea that have been described. The patient died in a state hospital for the insane to which he had been committed. The patient whose history has been described in Case V furnishes a good example of the insomnia, hyperkinesia, and disturbance in behavior seen in younger patients with encephalitis.

PAROXYSMAL YAWNING, INCESSANTLY REPEATED, AND PARKINSONIAN SYNDROME

Case VI.—A man aged thirty-seven years came to The Mayo Clinic June 5, 1929, because of drowsiness and exhaustion. He had had influenza in 1919 but apparently had recovered. Five years before he appeared at the clinic he had noticed gradually increasing drowsiness and a desire to sleep anywhere at any time. Three years before, vomiting without nausea had appeared and he had vomited after breakfast, daily, for more than a year. This had decreased gradually, and finally had disappeared. Mental activity had become reduced, weight had been lost, and all movements had become slower. Two years before he came to the clinic, yawning had appeared which might come fifteen or twenty times a minute at frequent intervals during the day. Exhaustion, slowness of movement and lack of mental concentration had been steadily increasing up to the time of his visit to the clinic.

Examination showed the patient to have a well marked parkinsonian syndrome. He yawned cavernously every few minutes and several times a minute. With each yawning movement an inspiratory gasp did not occur, but the jaw moved downward in a rotary fashion, unaccompanied by stretching or contraction of the muscles of the neck.

The condition was relatively mild in Case VI, and the gaping of the mouth was not so extreme as in other cases. Grunting noises are common in these chronic cases of epidemic encephalitis. In one case the condition was associated with marked compulsion to drink water, and as much as 60 liters were consumed in one day. These encephalitic cases of polydipsia and polyuria differ in some way from the usual case of diabetes insipidus. Their condition is not so readily controlled by administration of pituitrin, and the water hunger of these patients resembles the air hunger of others with its accompanying hyperpnea and breath-holding. Loud, sniffing expirations through the nose characterized the condition of one young girl seen at the clinic. The hissing noises were repeated many times a minute and could be heard throughout the hospital ward.

COMMENT

The pathogenesis of all these respiratory disorders is a vexed question. With the simple hyperpnea and myoclonic twitching of the diaphragm and intercostal muscles, a disturbance of the repiratory center in the medulla has been postulated. However, the vast majority of respiratory disturbances in epidemic encephalitis are too complex and too much associated with emotion and conscious effort and volition to be so easily explained. Respiration is in the main an automatic function, but can be influenced by conscious effort. In nearly all cases of respiratory disturbance during the course of epidemic encephalitis, the defect is in the automatic sphere and the conscious, voluntary control of breathing is affected to a much less extent. Although automatic breathing is normal during sleep, its disturbance causes considerable loss of rest and intractable insomnia. Emotional influences play a marked part in increasing the patient's difficulty; there seems to be an exaggerated effect of the normal

influence of emotion on the respiratory cycle. It is surprising how frequently respiratory disorders in encephalitis are associated with companion disorders of emotion and behavior. Marked psychomotor activity was common in the cases that have been reported.

Furthermore, the large number of children and adolescents affected (Fig. 214) suggests that, with their immature mechanisms of psychomotor control and labile emotional make-up, they

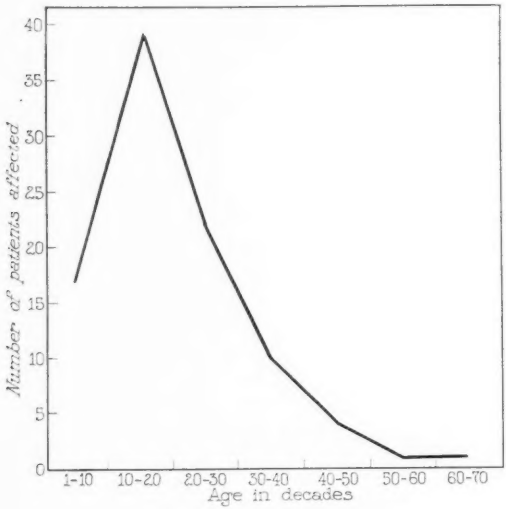


FIG. 214.—Age incidence.

are an easier prey to disturbance of respiratory function during the course of epidemic encephalitis. Certainly the level of disturbance in the central nervous system must be far higher than the medulla. Another viewpoint is that which takes in the compulsion features of the disease. As has been mentioned, the patients seem to possess a craving for air, and to hold it once it is obtained. Similarly, there is a strong desire to pour into the system as much water as it will hold. Yet in each case there is some degree of voluntary control, and obvious physical symp-

toms do not follow abstention. A patient with encephalitic respiratory hyperpnea does not die from suffocation if he breathes as a normal person would breathe, nor does a water drinker become parched and dehydrated as does the patient with true diabetes insipidus. Compulsive thinking and acting have been described in encephalitis, and failure to act on these compulsions would result in mental suffering as well as fear. The interesting feature is that there are all gradations between simple, automatic movements through compulsive movements to typical compulsive thinking with no sharp line to show where the physical ends and the psychic begins. Altogether, the explanation of these respiratory disorders is not a simple feat, the anatomic basis has not been worked out, and the problem must be regarded as far from being settled.

The diagnosis of these cases rests on their startling similarity to each other, and more than that, on accompanying evidences of chronic encephalitis, especially the parkinsonian syndrome. Seldom are these respiratory disturbances a solitary manifestation of epidemic encephalitis. When they are combined with insomnia, disorder in behavior, marked restlessness, parkinsonism, and so forth, and when they are present in all their persistence and consistence, recognition is usually easy. Sometimes a diagnosis can be made before the patient is even seen, by the characteristic, noisy breathing. The prognosis depends on the degree of encephalitis, as shown by accompanying signs of the disease. Respiratory disturbances themselves tend to disappear after months or years. In some cases they have remained stationary for eight years, but they themselves never cause death, although they are of extreme chronicity. Death, or invalidism, is more likely to result from some other syndrome, such as that of Parkinson's disease, and several years before death the respiratory disturbances may have passed off completely. In any case, the prognosis depends on the severity and progressive qualities of the chronic encephalitis, in which the respiratory syndrome is only a small part of an extremely complicated, widespread, pathologic process in the brain. As far as treatment is concerned there is no specific remedy. General care and isola-

tion from disturbing emotional influences are to be recommended, together with some sedative drug, such as phenobarbital or hyoscine. The difficulty is in the necessity of giving these drugs to full doses or overdoses before much result is attained, and frequently one has to choose between the disagreeable toxic influence of the drug in overdosage and the discomfort to the patient and relatives that the disease induces.

DISTURBANCES OF SLEEP AND MANIACAL DELIRIUM ASSOCIATED WITH SPONTANEOUSLY LOW BLOOD SUGAR; DELIRIUM FOLLOWING CONCUSSION; OBSESSION NEUROSIS WITH FATIGUE AND REGURGITATION OF FOOD; ENTERTAINING HALLUCINATIONS NOT INTERFERING WITH USEFULNESS; MILD MANIA ON RECOVERING FROM MYXEDEMA; A SUCCESSFUL AND CAPABLE MAN PROFOUNDLY DISABLED AND MADE EXTREMELY MISERABLE BY DEPRESSION; UNUSUAL MIGRAINE WITH DEPRESSION; NEURALGIC MIGRAINE; PERIODIC PARALYSIS OF EXTREMITIES; NARCOLEPSY AFTER SEVERE PNEUMONIA; RECURRING MYASTHENIA GRAVIS IN A BOY; UNUSUAL FAMILY HISTORY OF TRIGEMINAL NEURALGIA

LLOYD H. ZIEGLER

Neurologists and psychiatrists are accused by the medical profession at large of using long and more or less meaningless terms in the diagnosis, discussion and classification of unusual and interesting clinical phenomena. In presenting the following cases and in describing the diseases the simplest terms have been used. These cases were selected not only because of their interest from a neuropsychiatric standpoint, but because of the medical and surgical problems that were often associated. It is hoped that the cases may provoke further clinical research and studies directed to the etiology of the various biologic phenomena which cause distress, impair ability, and disrupt social and economic adaptation.

DISTURBANCES OF SLEEP AND MANIACAL DELIRIUM ASSOCIATED WITH SPONTANEOUSLY LOW BLOOD SUGAR

Case I.—A man aged forty-seven years, a contractor, was referred to The Mayo Clinic in October, 1928, because of an unusual malady of four

years' duration. His physician had seen a similar case at the clinic and suspected hypoglycemia. Except for the death of a sister from cancer, nothing of significance was elicited in the family history. He had had typhoid fever and mumps in 1902, smallpox in 1906, and influenza in 1919, without incident. He had always been a strong, robust man. His married life had not been happy and he had separated from his wife after living with her several years. The first symptoms noted were those of uneasiness, almost confusion, associated with weakness and sweating, which made it difficult to apply himself to his work. At first these attacks lasted only a few minutes and were infrequent during his work day, but after a year they were more severe and more frequent. At this time he discovered that eating a sandwich or drinking a cup of coffee with cream and sugar entirely relieved the attacks within a few minutes. All of his life he had slept well until a year after the onset of his illness, when his sleep began to be disturbed, by talking, walking, dreaming, and nightmares. He knew of these disturbances only by what his associates told him. Often in the second year of his illness he would awaken in the morning to find his room disarranged and concluded that he had had a nightmare. In August, 1926, after retiring, he walked from his apartment and on awakening found himself in another building. A month later he became "delirious and maniacal" at 3 a.m. and was taken to a hospital where he was surprised to find himself in restraint the next morning. Since that time he had had such attacks nearly every night unless he ate at intervals during the night. He felt that work and worry made the attacks worse. A short time before he came to The Mayo Clinic he was hospitalized in a psychopathic hospital. Food was refused him after 5 p.m. He was very restless and usually maniacal at night, but recovered from the attacks spontaneously by morning except for some confusion, lasting one to two hours. He had no memory whatsoever for any of the night attacks. At the psychopathic hospital "a nervous condition" was diagnosed.

Thorough study at the clinic has confirmed the patient's own observation about his condition. During the day if food was withheld two or three hours he became stuporous, sluggish, cyanotic, and appeared as if he had been awakened from a deep sleep. In this state he was aware of his surroundings, although on one occasion during the day when food had been withheld too long, he became unconscious and was overactive, talkative, and maniacal. In this state convulsions sometimes occurred. Either in the diurnal stuporous stage or in the nocturnal maniacal stage his blood sugar was very low (0.035 to 0.055 per cent) on every test and his condition returned to normal within half an hour after glucose was given by mouth or intravenously. Epinephrine had a similar effect. The maniacal attacks were more likely to occur at night if food was withheld.

General examination was essentially negative except for some slowness of response of the right pupil to light. The Wassermann reaction of the blood was negative.

In this case the blood sugar is low, and spontaneously associated with this (especially at night) there is delirium in which

the patient is very active and maniacal. The condition is relieved by the ingestion of food and the intravenous administration of glucose or epinephrine. This is a rare condition, in which psychosis and a disorder of metabolism are concurrent. Psychosis is not always associated with spontaneous hypoglycemia, but it has been seen in several other cases. Hartman has recently described a case similar to this in which the patient had convulsions when the blood sugar became very low. He died in a psychopathic hospital, supposedly from epilepsy. Sevringhaus has made a study of the nervous and mental phenomena accompanying treatment by insulin. Just as aviators have an altitude ceiling beyond which they cannot fly without a tendency to become delirious, so doubtless there are limits to blood sugar (possibly other substances also) within which life is compatible and outside of which it is threatened and behavior sometimes markedly altered. Such psychosis might be called "deprivation delirium." Information gained from this unusual case suggests the possibility that an occasional episodic psychosis may have a disorder of metabolism as its etiology.

DELIRIUM FOLLOWING CONCUSSION

Case II.—A man aged seventy-two years, a carpenter, was brought to The Mayo Clinic in a comatose condition. He had been born in Norway, but had spoken Norwegian very little since coming to this country in boyhood. He had been perfectly well until about three weeks previously, when he had been struck by an automobile and had suffered a concussion. He had been comatose since the accident. Roentgenograms did not reveal evidence of fracture of the skull, but the ninth and tenth ribs on the right side were fractured. His neck was very stiff, but evidence of fracture of the spine was not obtained. He was greatly emaciated due to the difficulty in taking food. Blood urea was 56 mg. for each 100 c.c. Pressure of spinal fluid was 5 cm.; it dropped to 4 cm. on removal of 6 c.c. of fluid. The fluid contained fresh blood (probably from the puncture). A left Babinski sign (dorsiflexion of great toe on plantar stroking) was thought to be present at times. He was incontinent of urine and feces. A nourishing diet by tube and much fluid were given. After being in the hospital a few days he began to scream and make unintelligible utterances. Hot packs were applied to the neck. Soon he tried to get out of bed and groped about unaware of anything in his environment. After being in the hospital about two weeks he began to speak Norwegian and he spoke of events apparently of the far past. After three weeks he began to inject an occasional English word into his utterances. Gradually he spoke more and more English. A little more than a month

after hospitalization he began to be aware of his surroundings but had no knowledge of the injury or of being brought to the hospital. He has recovered completely.

The interesting aspect of this delirium is its apparent relation to the patient's life. In coming out of the coma he first spoke Norwegian, the language of his boyhood. Gradually Norwegian was replaced by English, after which he became aware of his environment, but without memory of the accident or much of his convalescence.

OBSESSION NEUROSIS WITH FATIGUE AND REGURGITATION OF FOOD

Case III.—A woman aged twenty-nine years came to The Mayo Clinic because of vomiting and nervousness of three months' duration. Her father had used alcohol to excess. She had always vomited easily and always slept lightly. She was happily married and her husband was successful in business, in which she assisted him. In her work she was obsessed by the necessity for order, neatness, and cleanliness. She had in the last year gradually become more and more fatigued, and her work and some worries bore down on her more heavily. Three months before, she began to notice a strange feeling come over her suddenly which she described as being estranged about directions of the compass and yet knowing them. These feelings would leave her nearly as suddenly as they came. She was annoyed by them and dreaded them. At their onset she began to regurgitate food one to two hours after meals. She did not become nauseated. She had lost weight and appetite. She declared that the strange feelings of being lost and the vomiting were worse when she was fatigued or under more than average strain, which was also associated with a desire to scream or tear her clothing, neither of which she did. She stated that she became disgusted easily over food which might not seem entirely clean, and could not eat that kind of food for a long time. General medical and neurologic examinations were negative except for loss of 5 pounds in weight.

Regurgitation of food is often associated with various types of nervousness. In this case it accompanied the fatigue which came from responding to an obsession over cleanliness, order, and neatness. Doubtless her threshold of disgust, so closely related to vomiting and regurgitation, was lowered at these times. The fatigue which results from trying to relieve obsessions may be associated with various clinical phenomena, among which are anorexia of severe degree and vomiting. In another similar case the patient became exhausted, lost 40 pounds

in weight, and could not keep food on her stomach during a period when she was markedly obsessed by trivial things, which her better judgment told her were "silly." In still another case vomiting and anorexia occurred over an obsessive dread of meeting strangers socially. Surgery may be resorted to without avail although in such cases it is difficult to know without thorough neuropsychiatric study when dangerous surgical lesions are being overlooked and explained as a mere nervous manifestation.

ENTERTAINING HALLUCINATIONS NOT INTERFERING WITH USEFULNESS

Case IV.—A divorced woman aged thirty-eight years, a housekeeper for her father, came to The Mayo Clinic because of frequent sore throat, and to have an examination for a supposed "lump" in the right axilla. Her mother had died of cancer and heart disease. A history of mental disease in the family was not elicited. She had always been well and had worked reasonably hard. She finished the second year of high school at eighteen and remained at home until she married at the age of twenty-three. She had had one child who was living and well. Her married life was unhappy chiefly because of her husband's temper. They were divorced after living together five years. Seven years before coming to the clinic she had had a "fatty tumor" removed from the right axilla. She felt that it was recurring. She suspected that her tonsils were diseased. During the course of examination it was accidentally discovered that she got "messages from spirits." (She was not a spiritualist but an Episcopalian.) She declared that she had been hearing such voices for seven years. The voices told her pleasant things and in her isolated prairie home were what she called her "brain radio." She felt at times that they might be God's voice, although the topics were not necessarily religious. The voices would tell her things that might happen and thus were at times somewhat prophetic. She thought they might be the voices of friends and neighbors, but some voices were those of relatives several hundred miles away. They did not interfere with her work, although she admitted that she could hear them best when she was a bit sleepy or sluggish. She had thought at one time she might be going insane but after much deliberation convinced herself that they were "stray thoughts" which she had the power to pick up and felt herself fortunate in the isolation of her country home to be able to get such entertainment. She had also seen for several years a few pictures of things which she felt were associated with the "transferred thoughts." These were infrequent. She did not feel that she was being persecuted or mistreated. She did not sleep soundly. She was not anxious or depressed. She presented a normal appearance except for being a bit sluggish and indifferent.

The general medical and neurologic examinations, including that of the blood, were essentially negative except for evidence of infection of the tonsils. There was no recurrence of tumor of the right axilla.

This is an unusual patient, especially in view of the fact that she has had imaginations of hearing and seeing (hallucinations) of an entertaining kind so many years without much, if any, impairment of her ability to work. Socrates is said to have heard a voice, and at times Joan d'Arc heard voices. Francis Galton, in his "Inquiry into human faculty," gave a report of seemingly normal persons having imaginations of hearing and seeing. Horrax reported the nature of visual hallucinations as they occur in cases of tumor of the brain. Ormand spoke of several sane persons with visual hallucinations. In his cases the hallucinations were explained as most likely due to brain lesions. In the case here reported there was no clinical evidence of brain lesion. Although doubtless the patient has psychopathic tendencies she can work and enjoy life.

There are probably many persons who enjoy similar experiences. I know of a man whose hallucinations are usually useful to him in his highly skilled occupation, but at times become annoying. The fate of many psychopathic persons would be less unhappy if their hallucinations were entertaining and were not so distracting as to prevent occupational usefulness.

MILD MANIA ON RECOVERING FROM MYXEDEMA

Case V.—A woman aged fifty-eight years came to The Mayo Clinic in July, 1928, complaining of loss of strength and of nervousness of more than a year's duration. Nothing significant was elicited in the family history. She had always been well. She had been talkative, jovial, energetic, and happy and was considered the "life" of all social events of her neighborhood. She had always been a light sleeper and was awakened by the least noise at night. She was observant, noticing the smallest details wherever she went.

The patient's illness was characterized by loss of strength, especially in the legs, loss of 30 pounds in weight, and intolerance to heat, with more than usual perspiration. The basal metabolic rates (+16 and +29), with the history and impressions gained during examination, resulted in a diagnosis of exophthalmic goiter, and subtotal thyroidectomy was done in August, 1928. The pathologists reported "hypertrophic parenchymatous thyroid gland." Convalescence was uneventful and she promptly gained weight and strength, and returned home. At home she continued to gain weight and by November, 1928, was 40 pounds above normal, and felt sluggish and unusually sleepy. She returned to the clinic. Clinical myxedema was obvious; the basal metabolic rate was −29. Desiccated thyroid was administered at once and as the basal metabolic rate began to rise, the patient became very

restless, talkative, distractible, rambled in her conversation, and showed flight of ideas. The push of talk and activity was out of the ordinary. She was not depressed. She declared that to maintain her normal contact with the environment she continually had to make an effort in speech and activity, which were thus increased. She felt that her threshold of excitability had been lowered. As the basal metabolic rate approached normal, her normal personality returned and she lost the excess weight (chiefly edema). She was not depressed except for short intervals just before she became normal when she wept at times and declared that she was lonesome.

In this case, in which the patient was always talkative and energetic, myxedema served to depress natural tendencies to expression. On releasing this depressing influence by elevating the basal metabolic rate her natural tendencies to activity and talk became exaggerated and assumed the clinical proportions of mild mania. Rarely does one of Nature's experiments offer so fine an opportunity for the observation of the factors related to the evolution and dissolution of mild psychosis.

A SUCCESSFUL AND CAPABLE MAN PROFOUNDLY DISABLED AND MADE EXTREMELY MISERABLE BY DEPRESSION

Case VI.—A man aged forty-one years, a contractor, came to The Mayo Clinic complaining of nervousness of about two years' duration. His father's cousin had been depressed. Other members of the family were apparently well and capable. He had always worked hard to the exclusion of hobbies and play, and had been efficient. He took the hardest jobs and was known as the "trouble man." He had amassed a fair fortune. Two years before he began to worry over his business. This was unusual for him. His better judgment told him it was foolish and that things were all right. Some trouble with a partner, which he would have shaken off easily before, annoyed him. He became acutely upset at the funeral of a friend, had a severe headache for four days and subsequently became so downhearted that he feared for his own life. He disposed of a pistol and a razor. His thoughts came to him rapidly, he slept very little, and had such unpleasant feelings that he declared he had no words to describe them. He became fatigued easily whereas before he had been a giant of strength and endurance. He had the dreadful feeling that some calamity to himself and his family might happen at any time. He disliked meeting his friends and acquaintances. Before he became ill he had been a friendly and sociable man. Medicine did not relieve him. He felt unable to seek medical help away from home. Nothing interested him as it had before. About two years after the onset he began to have short periods in which he felt somewhat natural. He gradually improved and got entirely well. General medical and neurologic examinations were negative except for infected teeth and tonsils.

Such cases are not infrequently met in general practice. Many of the patients refer part of their distress to the heart, lungs, stomach, or some other part of the body. Such parts of the body may not show signs of organic disease, but the patient in his terrible distress may convince the physician that he has serious organic disease. Operations are not infrequently performed for the relief of such distress, usually without success. It behooves physicians to know the emotions, especially those giving rise to distress, such as depressions, anxiety, and a host of others that patients can describe poorly, if at all. Many such patients get well. A physician who understands such a patient and his distress and some ways of giving relief is greatly appreciated. Such disorders are not necessarily found among the deficient and inferior. They are found, as in this case, among the most capable and successful.

UNUSUAL MIGRAINE WITH DEPRESSION

Case VII.—A man aged fifty-six years, a manufacturer, came to The Mayo Clinic because of nervous attacks which he had had for many years. His father had had attacks of pain in the head associated with swelling over the eyes. His mother had "bilious attacks." At the age of sixteen years he had a sickness of six weeks' duration, with delirium at times, resembling typhoid. At the age of twenty he began to have occasional sick headaches lasting from one to six days. They rarely kept him from work. The ache was dull, throbbing in nature, in the occiput, and progressed in crescendo fashion to a climax which he characterized as a peculiar feeling originating in the epigastrium and radiating to the penis, rectum, and head, during which he vomited, had a bowel movement, and an ejaculation of semen. He would also break out in profuse perspiration. Following these, he was relieved and soon recovered, and remained well until the next attack. At the age of fifty-one these attacks began to be especially severe and prevented work. The headaches were replaced by a feeling of confusion, and restlessness and insomnia, because of which he feared he would lose control of himself. For years there had been a burning sensation of the whole body in attacks which had gradually grown worse. Between attacks he was a capable and able worker. He had consulted many physicians and, from advice he received, concluded that he would lose his mind. He was depressed over the possible outcome of his strange malady. The general and neurologic examinations were negative except for acne rosacea. More recently he has been getting along well with a more hopeful and better understanding of his attacks.

It is not unusual for migraine syndromes to undergo changes

between the ages of forty-five and fifty-five years. They may become worse, pass away, or change their character so completely as to baffle the understanding of the patient and his physician. This patient, from the many opinions gleaned from physicians, feared for his mind and was discouraged. His migrainous syndrome was so unusual as to be difficult of recognition and migraine of any kind remains one of the disorders of which so little is known from an etiologic standpoint.

NEURALGIC MIGRAINE

Case VIII.—A man aged thirty-seven years, a gasoline filling station operator, came to The Mayo Clinic on account of attacks of pain chiefly in the left side of the face for eleven or twelve years. His father and sister had had sick headaches. At the age of seven years he began to have attacks of bitemporal headache every month or two. His father had observed that the day before his headache began he had a ravenous appetite and ate far too much food. When the headaches began he would lie down wherever he happened to be and sleep one to two hours, after which he seemed relieved. These headaches continued until he was eleven years of age, following which he had them infrequently and chiefly after oversleeping. At the age of twenty-five he began to have attacks of severe pain in the left supra-orbital ridge. The attacks would last from a few weeks to several months, with free intervals of several months to a year. The pain was usually at night but would not occur every night. The pain was sometimes replaced by generalized headache; it was a severe, throbbing ache, punctuated by occasional stabs and it radiated to the left ear, left side of the neck, and chest, especially just before becoming quiescent for the night. During the pain perspiration poured from a circular area 3 cm. in diameter over the left supra-orbital ridge. Just before it ceased, a large amount of mucus dropped into the left nostril, following which the patient slept for an hour or two and was relieved. Medicine did not relieve him; wearing glasses and the extraction of teeth had not been of any benefit. There were no sensitive zones in which the pain could be induced by rubbing or irritation.

Fundoscopic examination revealed a small patch of inactive choroiditis in the temporal periphery of the left eye. Roentgenographic and clinical examinations of the sinuses were negative. One tooth was infected at its root. The spot over the left orbit was seen to perspire profusely in an attack. Roentgenograms of the head and the neurologic examination were entirely negative.

A man with a history of migraine in his family and with migraine earlier in life had attacks of severe pain chiefly at night over the left orbit with radiation to the left ear and left side of

the chest. With this history, the absence of a demonstrable lesion, and with a history of good health between attacks, the possibility of an unusual form of migraine, sometimes called neuralgic migraine, is most probable. These patients are in great distress; they seek relief on every hand; they consult many physicians. Because of the site of the distress, sinus or nasal trouble is suspected. These patients not infrequently have had their tonsils, adenoids, and teeth removed, and sinuses punctured and drained without relief. Occasionally the patient has had a more radical operation designed to relieve tic douloureux, without success. The patients are usually eager to have anything tried and may resort even to habit-forming drugs. This represents a type of distress of which medical science knows little.

PERIODIC PARALYSIS OF EXTREMITIES

Case IX.—A man aged twenty-three years, a truck driver, came to The Mayo Clinic complaining of attacks of recurring paralysis of the arms and legs for three years. His family were well except a brother who had migraine. The patient's first attack came on while he was asleep. He could barely wiggle his fingers and toes, and could not turn in bed; sensation seemed to be normal. Paralysis was of the flaccid type. He did not eat or drink in the forty-eight hours the attack lasted. He recovered in about two hours. He did not urinate or defecate in the attack. The next attack came six months later, during the day while he was on a train. He felt his arms and legs getting stiff for about four hours, after which he was completely paralyzed, and remained so for about forty-eight hours. The next attacks came three months apart, and during the last year they came every one to two months. He had noted, prior to the onset, a slight tingling sensation in the hands and feet for one to two hours, which warned him that an attack was coming. If he ate or drank in an attack, he vomited. He had urinated voluntarily only once in an attack. In the last year he had found that if he kept going, he could work through an attack in twelve hours, but if the attack went on to paralysis, it lasted forty-eight hours. He thought wrestling or hard exertion tended to bring them on. About a year after the onset of the paralysis he began to have attacks of severe frontal headache with nausea and vomiting, which were relieved by sleeping. Headaches came every month or six weeks and were independent of the paralysis. He was not worried, depressed or nervous. He was a capable young man of adequate personality. The neurologic examination, in his normal state, was negative except for sluggishness of the deep reflexes. Roentgenograms of the head, because of some digitations, suggested slight intracranial pressure. Pulse and blood pressure were normal.

This young man had seen many physicians. He had received various diagnoses, especially that of hysteria. Oppenheim described this condition as periodic paralysis of the extremities. It had been seen in association with malaria, but also independent of it. The etiology is not known. Few cases have been reported in America. Cases vary somewhat, but this case is fairly typical. A familial form has been described. No other member of this patient's family was so afflicted. The patient had attacks of migraine independent of the paralysis. Patients with migraine have been seen who had numbness and stiffness of the extremities. Whether the paralysis is on a migraine basis remains one of the problems of the future.

NARCOLEPSY AFTER SEVERE PNEUMONIA

Case X.—A man aged twenty-six years came to The Mayo Clinic seeking aid on account of attacks of sleepiness, which had bothered him ever since 1917, when he was fourteen years of age. There seemed to be nothing significant in the family history. He had had diphtheria in childhood, with uneventful recovery. At the age of fourteen, before the onset of the present illness, he had had severe pneumonia with delirium. In 1918, at the age of fifteen, he had had a mild attack of influenza for only a few days. After the pneumonia he apparently gained weight rapidly and at fifteen years weighed 185 pounds. He also had frequent attacks of sleepiness and in some he would fall asleep for a minute or less. In others he could apparently work through the drowsy spell by effort and it would leave. He had fallen asleep riding a farm cultivator or driving an automobile, awakening to find himself a considerable distance from where he had been when last conscious. He had not had accidents, but came near it on several occasions. Drowsiness or sleepiness had always been a precursor of the attacks of unconsciousness. After sleeping a minute or less he seemed refreshed. When asleep he did not have convulsive movements, according to the testimony of his friends. However, when drowsy and about to go to sleep, he had noted at times some jerking movements and stiffness of the arms for a few seconds. In the beginning the attacks occurred many times a day, but were becoming less frequent. He slept well at night. When he did not get enough sleep at night, attacks were more frequent the next day. He dreamed rather pleasant dreams. His energy for work had been impaired very little, if at all. He had noted that at times when he wanted to laugh about some amusing incident that he could not do so because the muscles of his body would become stiff and prevented laughing. He had not fallen in anger, laughter, or attempts to throw objects. He had found that drinking much coffee had helped him.

General and neurologic examinations were essentially negative. The basal metabolic rate was −12. Roentgenograms of the head and sella turcica

were negative. The pulse rate was 64. The patient was moderately obese, weighing 195 pounds; he had weighed 220 at one time.

This is a case of narcolepsy. Such cases are apparently increasing in numbers since the influenza epidemics of the last ten or eleven years. Gelineau first named the disease in 1880. The attacks may resemble petit mal except that sleepiness and drowsiness precede the loss of consciousness. Convulsive movements do not occur in the unconscious state. The attacks usually refresh the patient. Disturbance of motility accompanies emotion, such as anger and laughter, attempts to throw objects, or to make sudden violent movements. Patients sometimes fall to the ground in such emotion (motor disturbances). Obesity is common. The etiology of the disease is not known. In some cases the condition has followed closely after attacks of epidemic encephalitis. Others are to be found without an elicitable antecedent history of infection or trauma. Coffee drinking has seemed to be as good a remedy as patients have found.

RECURRING MYASTHENIA GRAVIS IN A BOY

Case XI.—A boy aged fourteen years was brought to The Mayo Clinic in August, 1927, because of weakness and inability to walk, of six weeks' duration. He had had measles at the age of three years, and chickenpox at the age of four. In January, 1923, he had severe sore throat for two weeks, but recovered. In June, 1923, he first noted drooping of the left eyelid and double vision. He did not have his usual energy. He took "iodine drops" for six weeks and recovered entirely. In June, 1924, 1925, and 1926, he had similar attacks and recovered in the same way. He did not have fever. About May 15, 1927, he began to have double vision on looking upward, followed soon by drooping of the right eyelid so that he could not see without lifting the lid with his fingers. This lid was closed for one to two weeks and then improved. The left lid then drooped. At the same time he had cramps in the muscles of his arms and legs. About July 1, 1927, weakness began in all the muscles of the body. The tonsils were removed July 8. Muscles became weaker so that he could not walk or raise his arms to the level of his shoulders. He could not get up when lying down. The muscles of his jaws were so weak that he could chew only a part of a minute. Talking and swallowing were very difficult because of weakness. He seemed best after a night's rest. He slept well. He was well nourished. The pulse rate was 100; the temperature was 99.2° F. The lymph nodes of the axillas, and cervical, inguinal, and submaxillary regions were slightly enlarged. The muscles were so weak that he could do very little. The eyelids drooped. The

soft palate elevated very little in phonation. Speech had a nasal twang. The eyes could scarcely be moved in any direction, which gave to his appearance a peculiar stare. He could not count to 100 without exhaustion. The deep reflexes of the knees, ankles, and arms were present and equal. Sensation over the body was normal. The patient is much improved three years from the onset of the last attack.

Myasthenia gravis means merely severe muscle weakness. The onset is often in the jaws and patients complain that their jaws become weak and they cannot chew. Probably the next most common site is the eyes; drooping of the eyelids is common. The cause of the condition is unknown. Lymphocytoid structures have been found in clusters in the muscles of such patients. About half of these patients have an enlarged thymus gland. This patient's thymus gland was not enlarged, as determined by roentgenograms of the chest. The case is unusual in that it began so early in life and recurred each year in the late spring. It usually occurs between the ages of fifteen and fifty. Patients with this disease tend to recover spontaneously with rest in bed. Because the muscles of deglutition often are involved, the problems of feeding and preventing aspiration of food into the bronchi are of major importance. Recently Adson performed gastrostomy on a patient so profoundly afflicted that the muscles of swallowing were completely paralyzed. Feedings were instituted through the gastrostomy opening. The patient recovered. Patients so afflicted are not infrequently called "neurasthenics." The baneful influence to the patient, as well as the physician, of such indiscriminate use of the word "neurasthenia" is apparent.

UNUSUAL FAMILY HISTORY OF TRIGEMINAL NEURALGIA

Case XII.—A man aged seventy-seven years came to The Mayo Clinic complaining of attacks of severe pain in the left side of the face for twenty-eight years. A brother and two sisters had similar disorders. The onset of pain was sudden, involved the left angle of the mouth and radiated over the left upper and the lower jaws. The pain was short, stabbing, paroxysmal and excruciating. Duller pains came to the left side of the forehead. Touching the corner of the mouth, eating, talking, or getting into the wind would induce a severe attack of pain which consisted of several jabs at intervals of a few seconds for from one to ten minutes, and repeated at varying intervals. He used morphine two years for relief and stopped it of his own volition. He had received one alcohol injection of the two lower branches of the left tri-

geminal nerve fifteen years previous to examination, with relief for six months. Eighteen months previously, quinine urea injections had relieved him for a few days only. Subsequent injections often failed to relieve. Some anesthesia existed at the left side of the mouth, doubtless as a result of the alcohol injection. The prostate gland was enlarged and residual urine was present in the bladder after urination.

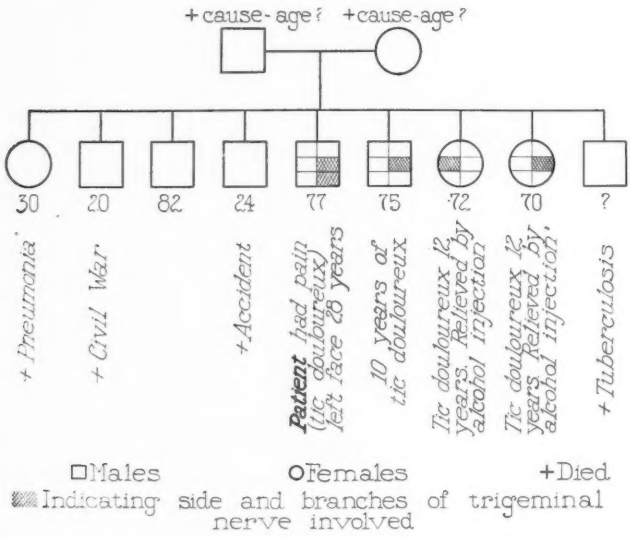


FIG. 215.

The patient was operated on and the sensory root of the left gasserian ganglion was cut. Convalescence was uneventful and the patient was entirely free from pain after the operation but with complete anesthesia of the left side of the face. The family history, as shown in Figure 215, is presented because of its unusual nature.

The unusual features about this case are the history of three other members of the family having the same disease. The disease does not usually run in families. Rarely, in recent times, does one see a patient who has had the disease for such a long time. Tic douloureux or trifacial or trigeminal neuralgia is a painful disease for the relief of which patients often have tonsils, teeth, and turbinates removed, and sinus operations, with-

out relief. There is no syndrome which it behooves nose and throat specialists and dentists to know more about in order to save the patient useless surgical expense and distress. The disease is very characteristic. The chief forms of relief are alcohol injection and surgical section of the sensory root of the trigeminal nerve, the latter of which gives permanent relief from the pain.

SPONTANEOUS PNEUMOTHORAX FOLLOWING BRONCHOSCOPIC ASPIRATION OF PULMONARY ABSCESS. REPORT OF THREE CASES

PORTER P. VINSON

BRONCHOSCOPIC procedures are very useful in the diagnosis and treatment of suppurative pulmonary diseases. It is particularly valuable in the treatment of both acute and chronic pulmonary abscess, and observers have recorded the resolution of chronic pulmonary abscess of many years' duration following a bronchoscopic examination with dilatation of a stenotic bronchus and aspiration of the contents of the abscess cavity. The discomforts and risks of bronchoscopic procedures are negligible, and complications following operation are rare. Because of the rarity of complications the following cases are recorded.

REPORT OF CASES

Case I.—A girl aged eight years had had a pulmonary abscess of undetermined origin for four years. The abscess was situated in the lower lobe of the right lung and there was a fluid level in the cavity (Fig. 216). On bronchoscopic examination a stricture was found in the posterior division of the bronchus to the lower lobe of the right lung. The stricture was dilated and the abscess cavity was thoroughly aspirated. A large amount of thin, watery purulent material, mixed with blood, was removed. The child was perfectly comfortable following the aspiration, but when the thorax was examined an hour after operation there was evidence of pneumothorax on the right side. Roentgen-ray examination the following day confirmed this evidence (Fig. 217). At the end of ten days the lung had reëxpanded completely (Fig. 218), but since the pulmonary condition remained the same it was decided to attempt surgical drainage of the abscess. At operation the pleura was not adherent at any point, the pleural cavity was free from effusion, and the former opening into the lung could not be identified. The patient died following the operation, although no attempt was made to drain the abscess. It was impossible at postmortem examination to demonstrate rupture into the lung.

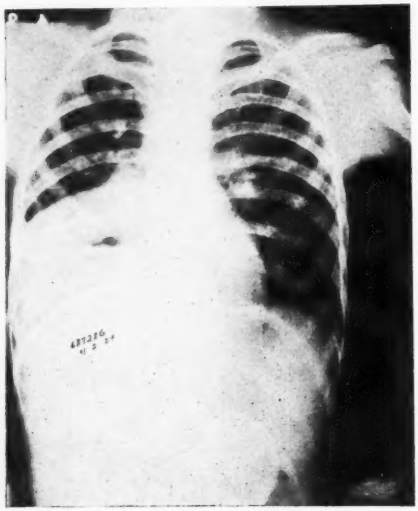


FIG. 216.—Chronic abscess of the lower lobe of the right lung; large cavitation and fluid level.

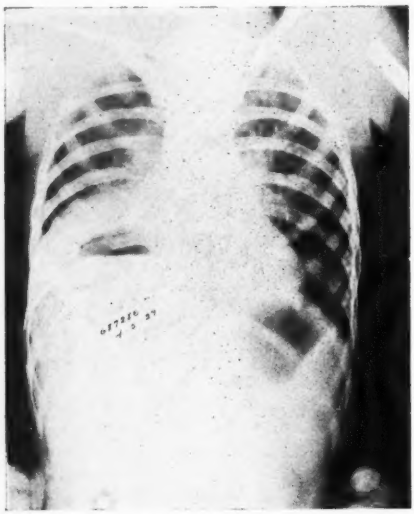


FIG. 217.—Partial collapse of the right lung following bronchoscopy.

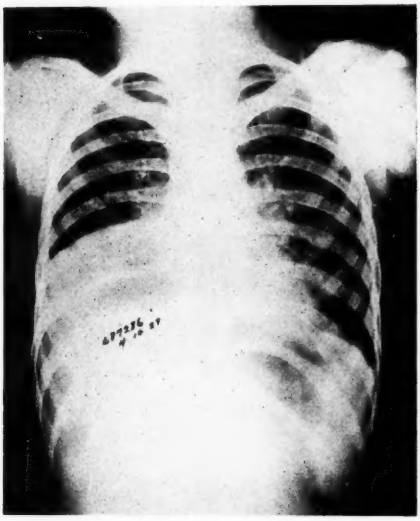


FIG. 218.—Complete reabsorption of air in the pleural cavity with pulmonary condition unchanged.

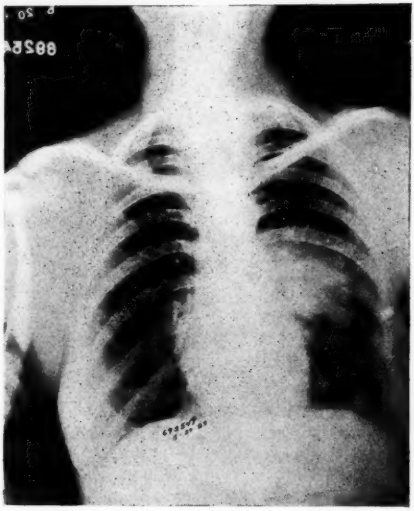


FIG. 219.—Chronic abscess of the upper lobe of the left lung.

Case II.—The patient was a woman aged twenty-six years. Following pneumonia four months previously, an abscess had developed in the upper lobe of the left lung (Fig. 219). Although her general condition was poor, it was decided to attempt bronchoscopic aspiration of the abscess. An aberrant stenotic bronchus was located in the left main bronchus, coming off posteriorly in the region of the bronchus to the upper lobe of the left lung. The bronchial stricture was dilated and thoroughly aspirated. Following the operation the patient was in a state of shock, but the next day she was much

FIG. 220.—Spontaneous pneumothorax with partial collapse of the left lung.

improved. Improvement continued, but on the fifth day after bronchoscopic aspiration she was found to have pneumothorax of the left side, with partial collapse of the left lung (Fig. 220).

Eleven days after the operation, purulent effusion developed, and aspiration was carried out, but the patient became progressively worse and died seven days later. At postmortem examination the left lung was very necrotic and it was found that the abscess had perforated into the pleural cavity.

Case III.—A man aged twenty-six years had had pneumonia eight years before examination at the clinic, and following this infection an abscess developed in the lower lobe of the left lung (Fig. 221). On bronchoscopic examination a very dense stricture was found in the bronchus to the lower lobe of the left lung. Forceps were introduced into the stricture, but it was not possible to introduce an aspirating tube through the area of stenosis.

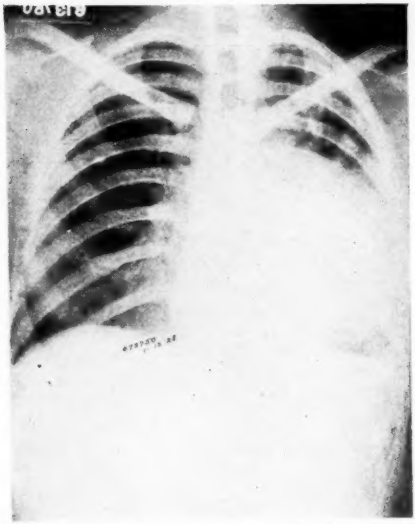


FIG. 221.—Chronic pulmonary abscess of eight years' duration.

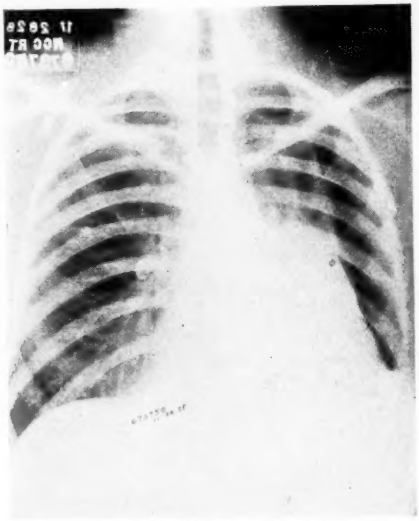


FIG. 222.—Partial pneumothorax following bronchoscopic aspiration of pulmonary abscess.

A week later the bronchoscope was again passed; the stricture was thoroughly dilated and the abscess was aspirated. Untoward reaction did not follow the instrumentation and although there was no evidence of pneumothorax save for a hyperresonant percussion note over the left side of the thorax, a roentgenogram made four days later showed partial left pneumothorax (Fig. 222).

At the end of a week the lung had almost completely reëxpanded. The patient returned for examination after an interval of two months and at

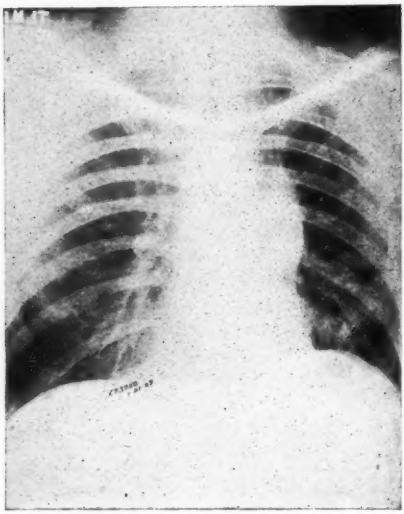


FIG. 223.—Marked resolution of pulmonary abscess.

that time he was practically free from pulmonary symptoms and had gained 15 pounds in weight. There was marked resolution of the pulmonary infiltration (Fig. 223).

SUMMARY AND CONCLUSIONS

Spontaneous pneumothorax may follow bronchoscopic aspiration of pulmonary abscess and unless roentgen-ray examination of the thorax is made after instrumentation it may be overlooked.

A tiny rupture of the lung occurs as the result of the coughing and straining associated with bronchoscopic aspiration.

In two cases (Cases I and III) rupture probably occurred in a normal portion of the lung, since effusion did not follow the perforation, and the lung had almost completely reëxpanded within ten days after the accident. In the other case (Case II) the original rupture probably occurred in an uninfected portion of the lung, since effusion did not develop until eleven days after instrumentation.

REASONS FOR URGING THYROIDECTOMY IN CASES OF ADENOMATOUS GOITER WITHOUT HYPERTHYROIDISM*

WILLIAM A. PLUMMER

THE classification of goiter used by H. S. Plummer, and which seems to be the most satisfactory from a clinical standpoint, is as follows: (1) Diffuse colloid goiter, (2) adenomatous goiter without hyperthyroidism, (3) adenomatous goiter with hyperthyroidism, and (4) exophthalmic goiter. This classification does not include inflammatory and malignant disease of the thyroid gland.

Adenomatous goiter differs from diffuse colloid goiter in that it consists essentially of nodular masses, adenomatous in type. Many large goiters which have the general contour of the normal thyroid gland, and therefore are believed to be diffuse colloid goiters, will be found to consist essentially of adenomatous nodules.

Diffuse colloid goiter is characteristic of the adolescent period, but may be present during adult life. Ordinarily in persons aged less than twenty years it is not considered a surgical condition, and in older persons it is seldom of sufficient size to warrant thyroidectomy.

Adenomatous goiter without hyperthyroidism is a surgical disease, but all easily palpable thyroid glands could not be considered surgical even though they might contain one or more small adenomatous nodules. A single adenoma, 3 cm. in diameter, in a thyroid gland which does not show evidence of diffuse enlargement, might well be considered surgical, whereas an

* Read before the Joint Councilor Meeting of the Second and Third Districts of the State Medical Society of Wisconsin, November 14, 1929.

adenomatous goiter which is gland shaped and contains multiple but small adenomatous nodules might not be considered surgical even though it were larger than the single adenoma. The more nodular a goiter, the smaller the goiter need be to warrant surgical removal.

The rate of growth in the goiter and the age of the patient are also factors which determine the advice to be given. In an individual case of adenomatous goiter without hyperthyroidism there might be great disagreement as to whether the size and type of the enlargement, the age of the patient, or the rate of growth of the goiter were such as to warrant operation. The large, nodular goiter, however, is generally conceded to be a surgical disease, whether it consists of multiple adenomas in one or both lobes, or a single adenoma. Nevertheless, patients having large adenomatous goiters are frequently told that operation is not urgent, and that it can safely be deferred until there is evidence of trouble from the goiter. Such advice, I believe, often is not justifiable.

The reasons for urging thyroidectomy in cases of adenomatous goiter without hyperthyroidism are: (1) the gradual, unrecognized development of signs of pressure; (2) the insidious onset of hyperthyroidism, and (3) the development of malignancy.

SIGNS OF PRESSURE

Physicians still see an occasional case of large, nodular goiter in which signs of pressure are so marked that they are noticed as soon as the patient enters the examining room. Evidences of obstructive dyspnea and stertorous breathing as the patient moves about are very obvious to the physician, although the patient may not complain of them. There may be an associated characteristic cough, and a peculiar quality in the voice which is difficult to describe, but which is not hoarseness such as results from paralysis or inflammation of the vocal cords. Signs of pressure to such a marked degree are evident to the patient and he has correctly ascribed them to goiter. However, these signs of pressure may exist in a minor degree for a long period of time and the patient will not be conscious of them. The

very slow growth of the goiter in such cases probably accounts for this. Slight obstructive dyspnea may be present, although not noticed by the patient, or if noticed it may be ascribed to overweight, or age, until after operation, when an increased sense of freedom in respiration proves that slight obstructive dyspnea existed previous to thyroidectomy. A sense of pressure in the throat is usually a nervous symptom, associated with exhaustion, anxiety, and so forth. A sense of pressure may result occasionally from the goiter itself, and usually is present only when the head is in certain positions: when the patient is reclining or working with the arms above the head.

In many cases the characteristic stridor may be demonstrated, although it is not noticeable during normal respiration and the patient has previously been unaware of it. The peculiar tone due to pressure can be elicited if the patient inspires quickly with the mouth open. Frequently this is also noticed during the short inspiration which follows laughing. Recently a patient was dismissed from my care whose case exemplifies the points I have just considered.

Case I.—A woman aged twenty-nine years had noticed that she had a goiter for five years. It had gradually increased in size. Her general health was good. Symptoms ascribed to the goiter had not been noticed except that when she was lying down it was necessary for her to adjust her head on the pillow to prevent a tight sensation. She had not noticed unusual dyspnea on exertion. The basal metabolic rate was −2 per cent. At the time of operation the right lobe was found to be of normal size, but the left lobe contained a nodular goiter, which was resected. The pathologic report was "multiple, hemorrhagic, fibrous, hyaline, degenerating colloid, and fetal adenoma." The specimen weighed 78 gm. and measured 8 by 6 by 4 cm.

At the time the patient was examined, previous to operation, it was noticed that the goiter had approached the median line and displaced the trachea to the right. The displacement was very evident, also, in the roentgenogram of the thorax. Definite stridor was noticeable when the patient inspired quickly with the mouth open, and it was also apparent during the quick inspiration which followed laughing. The patient did not seem to recognize any abnormal sound on inspiration previous to thyroidectomy, but on her return to the examining room for examination ten days later, she was highly elated because the peculiar sound had disappeared. Stridor could not be elicited. Roentgenograms of the thorax showed that the trachea had assumed a normal position. The patient stated that since operation she had been aware of increased freedom of breathing, although she had denied having

any dyspnea previous to operation. The goiter was not unusually large, as may be seen from its weight and measurements, and it was only slightly noticeable on inspection previous to operation.

Constriction of a bilateral adenomatous goiter will produce signs of pressure. However, as in this case, the absence of balance resulting from the presence of a nodular goiter confined to one lobe of the thyroid gland frequently creates displacement of the trachea, with accompanying signs of pressure, out of proportion to the size of the goiter. Such displacement is evident, not only on general examination, but in the roentgenogram. Pressure from an adenomatous goiter on one recurrent laryngeal nerve may interfere with nerve conduction, and laryngeal examination will show the corresponding vocal cord partially or completely paralyzed, frequently with little, if any, change in the patient's voice. However, unless the goiter is malignant, it rarely produces sufficient pressure on the recurrent laryngeal nerve to cause paralysis of a vocal cord.

INSIDIOUSNESS OF THE ONSET OF HYPERTHYROIDISM

A major danger in deferring thyroidectomy in cases of adenomatous goiter without hyperthyroidism is the long period of hyperthyroidism which may be present before the patient is conscious of any toxic symptoms. The following case is illustrative:

Case II.—A man aged sixty-eight years consulted the clinic five years ago. He had noticed the presence of a goiter for twenty years. He came to the clinic because several of his friends had advised him to have the goiter examined. He insisted that he was in good health, and that the goiter had not given him any trouble, except that for six months he had occasionally noticed a constricting sensation in the neck. His weight had not changed, he had not noticed heat intolerance, nervousness, or palpitation, and his appetite was normal, but he had noticed slight dyspnea on exertion.

The patient's appearance alone, in the examining room, would have warranted the diagnosis of hyperthyroidism. He appeared stimulated, and was sweating, symptoms so characteristic of hyperthyroidism. The blood pressure was 155 systolic and 80 diastolic, measured in millimeters of mercury; the pulse rate was 120, and the basal metabolic rate on two occasions was +31 and +33 per cent. Roentgenograms of the thorax and general examinations showed enlargement of the heart, graded 2. A diagnosis of adenomatous

goiter with hyperthyroidism was made. Although the patient's pulse had been regular previous to operation, auricular fibrillation of several hours' duration occurred on the second day after the operation. Transitory postoperative fibrillation after thyroidectomy is of frequent occurrence in cases of hyperthyroidism.

At the time of the patient's dismissal, three weeks later, his general appearance had entirely changed, and the appearance of stimulation had disappeared. Five years have elapsed since the operation. The patient is now in perfect health. He is seventy-three years of age and works every day. Although he admitted that he had been short of breath on exertion previous to operation, he now does not have dyspnea on exertion, palpitation or cardiac pain. Although he had not recognized any symptoms of ill health previous to thyroidectomy he now states that in view of the change which has occurred since operation, he was positive that the goiter had affected his health for ten or twelve years. During that time his hands and feet were always sweaty and he would perspire on slight exertion and felt stimulated. Since the operation, these symptoms have not been present. The patient, with whom I am well acquainted, is a successful business man, rather phlegmatic and emotionally very stable. His lack of any neurotic tendencies and the comparison he was able to make of his condition over a period of years and his sensations during a period of proved hyperthyroidism led me to believe that his statement with regard to his condition was correct.

This is not an isolated case. There have been many cases of hyperthyroidism in which the patient came to the clinic because relatives insisted that there was a change in his appearance and actions, yet he, himself, was not aware of ill health even though the basal metabolic rate was much above normal. Careful questioning after the patient has stated the approximate time of onset of symptoms frequently is convincing that hyperthyroidism had existed for several months or years previously. For instance, increased tolerance to cold may long antedate any uncomfortable symptoms.

The following case illustrates that it is not only possible for a patient to ignore symptoms of hyperthyroidism over a long time, but the physician may have difficulty in definitely establishing the diagnosis after thorough examination. Operation is thus inadvisably delayed. This is especially true in cases in which the clinical picture is complicated by symptoms of some other disease, or in which the metabolic rates are near the upper limits of normal.

Case III.—A woman aged forty-six years had had goiter for nineteen years. She had been ill much of the time during the ten years previous to her examination at the clinic, and it had been necessary that she discontinue work for several months at a time. Her history was one of anxiety neurosis or nervous exhaustion with innumerable unrelated symptoms. Close questioning, however, revealed that at the time of her visit to the clinic weakness and pounding of the heart were her chief complaints. Two metabolism tests a few days apart showed rates of +10 and +11 per cent. She had not recently taken iodine. The rates were somewhat discounted because of the patient's excitability, but apparently the tests were satisfactory. She had not recognized a change in tolerance for heat or cold. The diagnosis was neurasthenia, and colloid and adenomatous goiter with little evidence of hyperthyroidism.

Thyroidectomy was performed. The pathologists reported the thyroid tissue to be "multiple, hemorrhagic, fibrous, calcareous, degenerative colloid and fetal adenomas in a colloid thyroid gland." The third day after operation, auricular fibrillation developed and lasted several hours. Nineteen days after operation the basal metabolic rate was −4 per cent, and two days subsequently the rate was −2 per cent. These tests showed a definite drop in the metabolic rates after operation, in spite of the fact that the patient had not had a very satisfactory convalescence and was much more excited and hysterical at the time of the last metabolism test than she had been during any of the tests previous to operation. A letter received several weeks after her dismissal stated that her exhaustion was much less and that the pounding in the throat and head had disappeared. Another letter received eight months after operation indicated that her health had improved. It is true that this patient had not recognized the tell-tale symptoms of a change in tolerance to cold.

Patients with hyperthyroidism and persistent elevation of the basal metabolic rate do not tolerate warm weather and overheated rooms as well as they did previous to the onset of ill health. Antithetically, there is increased tolerance to cold which enables the patient to wear less clothing during cold weather, makes him want the rooms cooler than previously, and creates a tendency for him to put his feet out from under the bed covering at night. One usually obtains much more definite evidence of a change in heat and cold tolerance if, when the history is taken, the leading questions pertain to increased tolerance to cold rather than to a change in tolerance to heat. A definite history of increased tolerance for cold usually is one of the crucial points in diagnosis; however, this change in tolerance to cold frequently creates a sense of well being and there is occasionally a patient who has failed to notice the change.

Any major surgical procedure may be followed by transitory attacks of auricular fibrillation, under certain conditions, as in the presence of toxemia or disease of the heart not due to disease of the thyroid gland, especially in older persons. Such attacks, however, are particularly characteristic of the postoperative period in cases of adenomatous goiter with hyperthyroidism or of exophthalmic goiter. In the case I have just reported, that of a comparatively young woman without evidence of cardiac disease, I am convinced that the short period of auricular fibrillation following operation, the very definite drop in metabolism, and the subsequent course are indicative of previous hyperthyroidism. The diagnosis should have been adenomatous goiter with mild hyperthyroidism and neurasthenia. The case is illustrative and is not the only one in which a diagnosis has been changed after operation in view of postoperative fibrillation, a drop in metabolic rate, and the subsequent course of the case.

In this case the patient had basal metabolic rates of +10 and +11 per cent previous to operation, and before any iodine had been given. I might cite many cases of hyperthyroidism in which there was marked loss of weight and all of the characteristic symptoms of the disease, in which the metabolic rate was near the upper limits of normal. In many of these cases the patient's normal basal metabolic rate is probably unusually low, and a rate of +10 per cent in this group would represent definite hyperthyroidism. One case was that of a patient who manifested definite symptoms of hyperthyroidism, including loss of weight and increased tolerance to cold, and the metabolic rates were +2 and +9 per cent. A positive diagnosis of hyperthyroidism was made in spite of the low basal metabolic rates. Three weeks after operation the rates were −16 and −18 per cent without any signs of hypothyroidism. A letter from the patient a year and a half after operation reported normal health.

There are no available statistics to determine the frequency of mild but active hyperthyroidism in the presence of basal metabolic rates within the accepted normal range, but the in-

cidence is probably greater than is suspected. This possibility frequently makes it difficult to exclude the presence of hyperthyroidism in cases of adenomatous goiter. In exophthalmic goiter, also, the basal metabolic rates may be within the accepted normal limits, especially during those periods of remission so characteristic of the disease. The exophthalmos may become more marked while the basal metabolic rates remain within normal limits. However, in this disease the surgical problem differs somewhat from the problem which I am considering. In exophthalmic goiter the thyroid gland is not sufficiently large or nodular to warrant thyroidectomy until the constitutional symptoms are definite, except in very advanced cases and those in which the disease has been superimposed on adenomatous goiter. A questionnaire with regard to cases of adenomatous goiter in which the possibility of hyperthyroidism had not been considered previous to operation would reveal many patients whose subjective symptoms had improved after thyroidectomy. Such unsupported evidence as an indication of the presence of hyperthyroidism should not be accepted in view of the favorable psychic effects frequently produced by the removal of goiter. However, enough cases of adenomatous goiter in which the syptoms have been carefully analyzed before and after operation have been seen to indicate that it is not always possible to be certain of the diagnosis of hyperthyroidism previous to operation. The diagnosis of hyperthyroidism is not only difficult in the presence of functional nervous symptoms, but also in cases in which the patient is aged more than fifty years, when failing health may be ascribed to hidden malignancy, degenerative cardiovascular disease, and senility. Mild hyperthyroidism may eventuate in a break in cardiac compensation without the presence of hyperthyroidism having been considered, particularly in patients having cardiovascular degenerative changes. Angina pectoris may be aggravated by hyperthyroidism and yet the physician's attention may be so focused on the arteriosclerotic factor that the hyperthyroidism will exist unrecognized. Mild hyperthyroidism in the presence of severe benign or malignant hypertension may be difficult to diagnose. The insidious onset

of hyperthyroidism and the difficulty of early diagnosis justifies thyroidectomy before there is any reason to suspect the presence of the disease and while the patient is still in good health. The older the patient, the more dangerous it is to defer operation from the standpoint of hyperthyroidism. In 78 per cent of the cases of adenomatous goiter with hyperthyroidism observed at the clinic, the patient was aged more than forty years at the time of examination.

DEVELOPMENT OF MALIGNANCY

Pemberton, in collaboration with Broders and Bueermann, reviewed the cases of carcinoma of the thyroid gland observed in The Mayo Clinic from 1907 to 1926, inclusive. The material comprised 276 operative and 181 nonoperative cases. The frequency of carcinoma of the thyroid gland as compared with that of benign nodular tumors of the gland was 1 : 36.7 (2.7 per cent). These observers were of the opinion that there was unquestionable evidence that malignancy had developed in benign goiter in 87 per cent of the cases; the conclusion was based on an exhaustive review of the histories for evidence of preëxisting goiter and on examination of the specimens removed at operation. In 65 per cent of the 276 cases in which operation was performed the diagnosis had not been suspected by the clinician. In only 48 per cent of the cases was there a history of rapid growth of the tumor of two years' duration or less. The danger of the development of carcinoma in an adenomatous goiter increases with the age of the patient. The age incidence corresponds to that of carcinoma in general. In 69 per cent of the operative cases the patients were in the fourth, fifth, and sixth decades of life.[2]

SUMMARY

It must be admitted that there are adenomatous goiters which are too small, especially if diffuse, to warrant surgical procedures. It is assumed, however, that all are willing to concede that a nodular adenomatous goiter of any considerable size is a surgical condition even if hyperthyroidism is not present. In cases of patients aged less than thirty years, or possibly

forty years, there is no great danger in deferring thyroidectomy, and in individual cases, regardless of the age of the patient, there may be special reasons which warrant the indefinite postponement of surgical measures. Nevertheless, I feel that physicians sometimes agree too readily with patients in their desire to delay operation. I have endeavored to emphasize that it is not always advisable or safe to encourage this procrastination. Symptoms of pressure may develop so gradually that the patient is not conscious of them, and is perfectly happy with them, yet he may feel greatly relieved following thyroidectomy. Hyperthyroidism may exist for a long period without producing consciousness of ill health. Such a prodromal period, varying from weeks to years, is probably always present in cases of adenomatous goiter with hyperthyroidism. The diagnosis of hyperthyroidism is difficult early in the course of the disease. This is especially true in the presence of symptoms of some associated condition, particularly a functional nervous or cardiovascular disorder. Therefore, in cases of adenomatous goiter without toxic symptoms the insidiousness of the onset of hyperthyroidism is a logical reason for not postponing operation indefinitely.

The ratio of 2.7 per cent of cases of malignant tumors of the thyroid gland to those of all adenomatous and colloid goiters in which operation was performed at the clinic probably gives an exaggerated impression of the relative frequency of malignancy of the thyroid gland. Pemberton and Balfour called attention to this discrepancy: "Many patients with simple nodular goiter never seek medical advice, while all patients with carcinoma of the thyroid eventually come to the physician."[2] However, at the clinic we are constantly seeing cases of malignant adenomatous goiter. In the larger percentage of these cases operation has been performed before there was sufficient change in the size or character of the growth to lead one to suspect the nature of the lesion. This occurs with a regularity so disturbing that it justifies the urging of thyroidectomy in cases of adenomatous goiter before there is any reason to suspect malignant change in the tumor.

The older the patient, the greater the danger of postponing

thyroidectomy indefinitely, both from the standpoint of hyperthyroidism and of malignancy of the thyroid gland.

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CERTAIN CLINICAL AND TERMINAL PICTURES IN HEPATIC DISEASE

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OBVIOUSLY, jaundice and ascites, representing, respectively, obstruction to the biliary and portal system, are the two most common and familiar accompaniments of hepatic disease. These two cardinal manifestations, each with its associated clinical syndrome, are generally known, fairly well understood, and require little, if any, comment. Although these manifestations are striking in character, and often produce marked disability, so far as the patient is concerned, they are of themselves not necessarily of grave prognostic significance. Wangensteen recently reported a case of obstructive jaundice of three and a half years' duration, and called attention to another of sixteen years' duration reported by Sir Frederick Treves. Cases of hepatic cirrhosis with a history of ascites of similar duration and with ultimate recovery are also on record.

To a clinician, who has frequent or continuous contacts with large numbers of patients with hepatic disease, it soon becomes apparent that special syndromes frequently are superimposed on the initial clinical picture. These merit more general recognition and invite interpretation as to pathogenesis. Some of these clinical pictures which I am about to sketch are unquestionably known to many physicians, but I believe that they are not all familiar to the profession as a whole. In some instances they represent terminal clinical pictures and hence are of grave prognostic significance, and as such they deserve detailed discussion. Although we refer to separate syndromes, it must be recognized that the clinical picture, in any individual case, is often a composite one, in which the individual effects of several distinct processes are to be recognized.

With this point of view in mind I wish to present the histories of a series of cases of hepatic disease in which certain clinical phenomena stand out with such clearness as to have left definite and lasting impressions. In the first picture the narcosis in cases of insufficiency of the liver appears to resemble prolonged normal sleep.

Sleep, narcosis, or coma is seen frequently in the end stage of hepatic disease. At its onset the patient may appear to sleep naturally, although continuously. In this early stage he may be awakened, although he still appears sleepy and stuporous. Later the sleep becomes progressively deeper so that the patient can no longer be aroused by ordinary methods. The breathing may be normal in rate and rhythm. The patient is relaxed, flaccid, and may be placed in any position. He is neither dyspneic nor cyanotic. He looks comfortable and for a time as though narcotized or in a normal sleep. Nausea, retching, vomiting, stertorous breathing, Cheyne-Stokes respiration, and other symptoms so frequently encountered in uremia may all be lacking. Day after day the patient may continue to sleep until death supervenes. It is the appearance of normal sleep that is so impressive.

This narcosis is usually a late and a terminal phenomenon. It may constitute the closing chapter in any form of serious diseases of the liver and be superimposed on the clinical picture of the disease itself. Once firmly established, a fatal outcome is to be expected. Not infrequently, however, the patient may be roused to complete consciousness for a few hours by one specific measure, the intravenous administration of large quantities of glucose solution (900 to 1,200 c.c. of 10 per cent solution or 500 to 600 c.c. of a 20 per cent solution). This measure has been used effectively in more than one instance in which the family has been gathered from a distance to the bedside. The relatives have been told that the patient may be aroused temporarily for a few hours. At the appointed time the glucose solution is administered and the patient is rendered conscious for two to six hours. Gradually, however, sleep reasserts its control, after which nothing is of further avail. In the fol-

lowing case this narcotized state was present as a terminal phenomenon.

Case I. Chronic cholecystitis with stones; advanced cirrhosis of the mixed type.—A woman aged fifty years came to the clinic August 26, 1926, because of ascites. For sixteen years she had had biliary colic at irregular intervals. Jaundice had usually accompanied the attacks. Ascites had developed in June, 1926, following such colic. The ascites was so marked that paracentesis was necessary three times in the next six months.

The skin was dry and icteroid. The abdomen was enlarged and the patient presented the characteristic picture of cirrhosis. The serum bilirubin was 3.8 mg. for each 100 c.c. The bromsulphalein test showed marked retention of dye. The patient did not respond well to treatment with ammonium chloride and merbaphen; September 1 paracentesis was done and 9,000 c.c. of straw-colored fluid was removed. Shortly afterward her appetite failed and she began to refuse food. September 7 she was very weak, drowsy, and slightly incoherent at times. She continued to fail, and two days later fell asleep, was stuporous, and presented this typical picture of normal sleep or narcosis. After the arrival of her relatives she was given 500 c.c. of 20 per cent glucose in saline sodium chloride solution intravenously. She rallied for a period of a few hours, ate a little, and recognized the members of her family. The remission, however, was only temporary. She became comatose rapidly, and died two days later.

At necropsy, chronic cholecystitis with cholelithiasis, atrophic cirrhosis (1,230 gm.) of the liver, and extensive collateral circulation with ascites were found. This patient apparently had a mixed type of cirrhosis consequent on the long-standing (sixteen years) infection of the biliary passages.

The second picture is one of a tragedy that occurs all too frequently in certain forms of disease of the liver. This one occurred on a southern golf course and came as a great shock to the family and to his physicians.

Case II. Death from gastro-intestinal hemorrhage in a case of splenic anemia with portal cirrhosis.—A man aged forty-nine years was admitted to the clinic March 27, 1924, because of dyspnea, ascites, and edema of the legs of eight weeks' duration. There had been slight hematemesis in April, 1923. He had been well thereafter, although anemic all summer. In January, 1924, he had a series of profuse gastro-intestinal hemorrhages; the hemoglobin dropped to 11 per cent. He was taken to the hospital and a transfusion was given. A few days later edema appeared in the feet and progressed until the combination of the ascites and the edema of the extremities and scrotum produced a clinical picture as striking as it was pitiable. Another small hemorrhage occurred three weeks prior to the patient's admission to the clinic.

A diagnosis of splenic anemia with Banti's disease was made. A transfusion was given four times in the course of the first three weeks; a total of

1,800 c.c. of blood was given. The first day after admission paracentesis was done, with the removal of 12.5 liters of fluid. After paracentesis the liver and spleen were easily palpated. Throughout the period of hospitalization the patient was on a Sippy diet. The edema, which was marked on entrance, decreased somewhat during the first ten days. April 15 tarry stools were passed. The fragility of the erythrocytes was normal. Paracentesis was done again April 24, and 12 liters of fluid was removed. Throughout the period of hospitalization the fluid intake varied from 800 to 2,500 c.c. and the urinary output from 550 to 1,250 c.c. May 10 the hemoglobin was 40 per cent; erythrocytes numbered 3,600,000 and leukocytes 4,800. The output of urine continued to be small and the specific gravity varied from 1.014 to 1.018 from time to time. April 26, 1924, 900 milligram-hours of radium was applied over the region of the spleen, and a month later the spleen appeared to be reduced a third in size.

The patient was admitted to hospital May 22, at which time marked ascites and edema were noted. Studies of hepatic function showed moderate retention of dye, a positive levulose-tolerance test, an indirect van den Bergh reaction and serum bilirubin of 1.9 mg. for each 100 c.c. The hemoglobin was 47 per cent; the erythrocytes numbered 3,820,000 and the leukocytes 3,500. Paracentesis of the abdomen was again performed. After the paracentesis the margin of the liver was felt a hand's breadth below the costal margin. The edema of the legs persisted. Banti's disease, with a considerable degree of associated hepatic cirrhosis was diagnosed June 13, the condition of the blood was decidedly improved; the hemoglobin was 54 per cent and the erythrocytes numbered 4,400,000. The abdomen, however, was still distended and there was still some edema of the legs. The use of merbaphen was advised. Two doses were given intramuscularly (1 and 1.5 c.c.), with marked subsequent diuresis and a loss of weight from 211 to 199 pounds. After a third dose of merbaphen, the loss of weight was 20 pounds. Subsequently the edema cleared up entirely and the patient returned home in excellent condition, having gained remarkably in strength and spirits. He became active and played golf. There was no recurrence of edema and no ascites during the next six months.

A letter received from the patient's physician after his return home stated that the patient had an enlarged spleen extending 7.5 cm. below the costal border, but it was not painful or tender. The urine was clear, acid, with a specific gravity of 1.024; there was no albumin. The hemoglobin was 73 per cent; the erythrocytes numbered 4,600,000 and the leukocytes 4,800. A stained smear showed a slight variation in the size of the erythrocytes, but the cells were otherwise normal. The improvement continued and the patient remained in apparently excellent health until January, 1925, when he died suddenly in the middle of a golf game of acute gastro-intestinal hemorrhage and hematemesis.

This case illustrates both the danger and the tragedy consequent on present inability to control the development of esophageal varices as effectively as it is possible to control the

development of ascites in association with cirrhotic changes in the liver. An effort is being made to prevent such hemorrhages by ligation of the veins (left coronary) which contribute the blood to these esophageal varices. Ligation of this one vein alone does not suffice and, consequently, other veins must be ligated and an effort must be made to obliterate the varices by methods more in use to control varicose veins in the legs. Splenectomy proves a great protection against this complication.

The third picture reveals the development of many purpuric spots following the use of merbaphen in an attempt to control ascites in portal cirrhosis. This has been observed in a sufficient number of cases so that doubt no longer exists concerning the question of cause and effect.

Case III. Purpuric manifestations following the use of merbaphen; uremia in portal cirrhosis.—A farmer aged sixty-one years came to the clinic in August, 1927, complaining of swelling of the abdomen and legs of about two months' duration. The appearance of ascites had been preceded by indefinite abdominal distress and occasional mild attacks of diarrhea. A history of alcoholism was obtained. Paracentesis of the abdomen had been done once, and a large quantity of clear yellowish fluid had been removed.

The patient was weak and rather pale and there was a slight icteric tinge to the skin and sclerotics. The abdomen was greatly distended with fluid, and dilated veins were noted on the anterior abdominal wall. There was also moderate edema of the legs. The heart and lungs were essentially normal. Repeated urinalysis was negative except for a few hyaline casts. The hemoglobin was 65 per cent; erythrocytes numbered 3,650,000 and leukocytes 6,800. The Wassermann reaction on the blood was negative. The return of phenolsulphonephthalein was 45 per cent in two hours, and the blood urea was 38 mg. for each 100 c.c. The bromsulphalein test showed marked retention of dye. The serum bilirubin was 2 mg. for each 100 c.c. A direct van den Bergh reaction was obtained. Because of the patient's extreme discomfort, abdominal paracentesis was performed as an emergency measure, and 9,000 c.c. of amber colored fluid was removed from the peritoneal cavity. Following this, palpation did not reveal masses of any kind; the edge of the liver was palpable at the costal margin.

After paracentesis, the ascites accumulated rapidly, and within a few days it was decided to resort to the use of diuretics. The patient was given ammonium nitrate, 6 gm. daily, and two trial doses of merbaphen, 0.75 c.c. intramuscularly and 1 c.c. intravenously, without any untoward effects. There was no significant increase in the urinary output. Following the second dose the establishment of a striking clinical picture was witnessed. A few purpuric spots appeared on the dorsum of the left hand. A tourniquet test was weakly positive. The following day a new collection of purpuric

lesions was visible in the same area. The coagulation time and bleeding time and the platelet count were negative. On the following day the lesions were fading; the patient's general condition was otherwise unchanged. Because of the mildness of this reaction it was decided to repeat the merbaphen four days later, and a dose of 2 c.c. was given intravenously. There was a slight diuretic response, 1,100 c.c. of urine being voided. Toxic effects were not noted, and careful search failed to reveal purpuric lesions. The second dose of merbaphen, 2 c.c., failed to produce either diuresis or toxic effects. Calcium chloride in doses of 2 gm. daily, by mouth, was also given at this time and the urinary output increased somewhat. December 27, eleven days after the initial appearance of purpura, a dose of 2 c.c. of salyrgan was given, and was followed by a very good diuretic response, the patient voiding 2,700 c.c. of urine in twenty-four hours. The only toxic manifestation was another group of purpuric lesions on the dorsal surfaces of the hands. The patient's digestion and appetite were somewhat disturbed, which was attributed to the oral ingestion of ammonium nitrate and calcium chloride. Attempts at diuretic treatment were abandoned temporarily and the patient was placed on a bland diet. The ascites increased slowly, and since the patient had to travel a long distance to his home, paracentesis was resorted to. The ascitic fluid continued to accumulate rapidly while he was at home, so that paracentesis had to be done at approximately weekly intervals.

The patient returned to the clinic May 28, 1928. His physical condition was essentially unchanged from that on the first admission. He was slightly more anemic; the hemoglobin was 55 per cent, and the erythrocytes numbered 2,810,000. The blood urea was 49 mg. for each 100 c.c.

Because of marked distention paracentesis was done June 1, and the patient was then put on a rigid salt-free diet and was given ammonium nitrate. June 7 he was given 2 c.c. of salyrgan intravenously without any diuretic response. June 21 the salyrgan was repeated, without effect. The following day purpura again appeared; an extensive group of purpuric spots was visible on the hands and, to a lesser extent, on the feet. A tourniquet test at a pressure of 85 mm. for one minute caused a striking response. Merbaphen was not given further, but another group of purpuric spots at the dorsum of the hands appeared July 11. The platelets numbered 104,000 and the fragility of the erythrocytes was not changed from the normal.

The patient's condition continued to be extremely serious, although striking changes did not occur. The serum bilirubin varied between 1.8 to 3.7 mg. for each 100 c.c. In spite of stringent restriction of fluid the specific gravity of the urine remained at a level of 1.009 to 1.016, and the blood urea varied between 65 and 111 mg. for each 100 c.c. The urinary output varied between 250 and 750 c.c., and was not affected by any of the usual diuretics. A moderate degree of renal insufficiency was present, thus manifesting incipient uremia in association with severe portal cirrhosis, as well as purpuric manifestations apparently following the use of merbaphen.

Cases II and III illustrate two types of bleeding seen in association with hepatic disease. The danger of postoperative

hemorrhage in patients with a prolonged coagulation time of the blood is well known.

The fourth clinical picture is one of a peculiar type of mental disturbance, disorientation, and excitement, following the use of ammonium salts in the treatment of ascites in a patient with marked portal cirrhosis. Although it is not proved that this disorientation is entirely due to ammonium poisoning, yet the picture has been encountered in hepatic disease sufficiently often under treatment with ammonium salts to raise the question and to demand an answer.

Case IV. Disorientation and excitement following the therapeutic use of ammonium salts in a patient with marked portal cirrhosis.—A woman aged fifty-six years, came to the clinic January 15, 1926, because of ascites which had developed two months previously. Paracentesis had been done three times since then. The previous history was essentially negative, although she had experienced one or two periods of mild diarrhea and a slight amount of belching, together with moderate loss of strength and weight during the preceding year or so. There had been no pain or jaundice.

When the patient was admitted to the hospital, marked ascites was present. The spleen was enlarged, but the liver could not be felt. She improved under treatment with ammonium chloride and merbaphen, and was free of ascites when dismissed from the hospital February 2. The fluid gradually recurred and she returned April 21. At this time the spleen was palpable 5 cm. below the costal margin, and the edge of the liver was 6 cm. below the costal margin. There was moderate ascites. The hemoglobin was 75 per cent and the erythrocytes numbered 4,380,000. The serum bilirubin was 0.9 mg. There was marked retention of bromsulphalein.

The patient was given a course of ammonium chloride for seven days, without any marked diuresis. She was then given ammonium nitrate for two weeks, without change. Injection of merbaphen, May 11, only increased the urinary output from 300 to 750 c.c. May 13 she refused food, seemed to be disoriented and confused mentally, and was very tired and exhausted. The next day she was very drowsy, difficult to arouse, and rapidly became stuporous. Stimulants were given, more fluid was allowed, and the intake of carbohydrates, especially of glucose, was forced. She gradually improved, and May 19 seemed much brighter and more normal mentally. Ammonium chloride was again administered. May 25 the patient became extremely restless and slightly irrational. She turned from side to side in bed, yawned much, and there was marked trembling and shivering. Later she again became comatose, but continued to be restless, with marked muscular twitching. The blood urea increased to 114 mg. for each 100 c.c., but the alkali reserve did not fall below 60 volumes per cent. The ammonium chloride was discontinued. Urinary retention was relieved by catheterization. The blood urea decreased slightly and the mental symptoms cleared up. This improve-

ment was temporary. Three days later she went into a state of quiet stupor and died June 4 in deep coma. At necropsy marked portal cirrhosis of the liver with splenomegaly and ascites was found.

The patient in this case clinically presents the ordinary type of portal cirrhosis, and the terminal picture was that of hepatic insufficiency with coma, which has been emphasized. The clinical picture of disorientation and marked irritability between May 25 and June 1, however, was most unusual and was strongly suggestive of intoxication arising from the use of ammonium salts.

Psychic disturbances are not common, but they occasionally accompany the treatment of portal cirrhosis with ascites by means of ammonium salts and organic mercurial diuretics according to the method of Rowntree, Keith, and Barrier. The symptoms are restlessness and sleeplessness, and may be accompanied by nausea. The patient is disoriented as to time and place, loses track of events, and later recalls them not at all or only in the most hazy way. As a part of this restlessness and excitement he frequently wants to be up and wanders about, so that an attendant must be constantly at hand. Fortunately the patients do not become violent and restraint has not been necessary. These periods of disturbance are of short duration, disappearing in one or two days after the treatment is stopped, although the recovery may be spontaneous.

The cause of this variety of intoxication has not been determined. It has only been observed in patients with advanced portal cirrhosis and does not occur following the treatment of other forms of edema or ascites by the same method. The mercurial diuretics used, merbaphen and salyrgan, do not seem to be implicated. Clinical observation indicates that it is most closely associated with the administration of ammonium salts to patients with marked hepatic injury. Even here it does not occur with sufficient frequency or severity to militate against the treatment of ascites by the method previously outlined.

Somewhat similar symptoms have been observed experimentally in animals. Hahn, Massen, Necki, and Pavlov studied dogs in which the portal blood was shunted around the liver by

means of an Eck fistula. The feeding of large amounts of meat to such animals often is followed by the appearance of pronounced toxic symptoms. The animals become excitable, and muscular twitchings develop which are followed by ataxia and later by weakness and coma. There is an associated disturbance of the sensorium and the animals may become totally deaf and blind. Death occurs either in coma or in clonic convulsions. Recovery from milder degrees of intoxication is rapid and complete. The cause of this intoxication by meat in the Eck fistula animal is a matter of controversy. The functional disturbance in the liver is an important element. Carbonic acid, ammonia, meat extract, and various disturbances in protein catabolism have been suggested as causative agents. More recently, Fischler ascribed the production of symptoms to associated alkalosis.

Frerichs in 1851 reported the development of muscular twitchings or convulsions in dogs following the intravenous injection of solution of ammonium carbonate. The possible relationship of these effects to the symptoms in uremia, parathyroid tetany, or the intoxication by meat in dogs with Eck fistula has led to the numerous investigations of Petroff, Marfori, Carlson and Jacobson, Trendelenburg, and others. The action is apparently independent of the anion, and similar symptoms follow the injection of the chloride or lactate as they do the injection of ammonium carbonate. The effect varies with the rate of administration and the quantity given. The reflex excitability is rapidly increased. Salivation, nausea, and vomiting occur. Twitching and tremors appear first in the muscles of the head and neck, but rapidly spread over the whole body and tetany or clonic-tonic convulsions supervene. Respiration is irregular. Death in convulsions may occur, but often the stage of excitement is replaced by one of depression, with somnolence and muscular weakness. Recovery is rapid and complete in those dogs receiving sublethal doses of ammonium salts.

Other work has indicated that the foregoing conditions, that is, uremia parathyroid tetany and meat intoxication are to be explained on other bases than that of poisoning by ammonia.

Similarly, there is no direct evidence that the symptoms in the case reported are due to poisoning by ammonia. The liver is concerned in the normal conversion of ammonium salts in the body into urea, and this conversion apparently is less complete after experimental injury to the liver. On the other hand, the administration of ammonium salts in therapeutic doses to patients with advanced hepatic cirrhosis does not produce significant increase in the content of ammonia in the blood.

An adequate explanation cannot be offered for the symptoms observed in this case. A direct analogy with the experimental observations is not to be drawn; nevertheless, these points of similarity afford much food for thought.

The fifth picture is that of anemia and uremia superimposed on hepatic insufficiency.

Case V. Choledocholithiasis, postoperative renal insufficiency with uremia in a case of chronic cholecystitis with stones and an obstructive biliary cirrhosis.—A man aged sixty-eight years came to the clinic October 18, 1928, because of jaundice of three months' duration. He had first noticed loss of appetite, increased fatiguability and loss of strength. The stools became clay-colored, the urine dark, and soon afterward clinical jaundice was observed. He did not have acute colics or chills, but he did have a dull aching pain in the epigastrium and along the right costal margin, with constant soreness on pressure. Pruritus was present at irregular intervals. He had lost a total of 45 pounds.

When examined the patient was thin and emaciated. The skin was markedly icteric. The liver was slightly enlarged, and the surface was firm, smooth, and slightly tender. The spleen was readily palpable just below the left costal margin. The superficial abdominal veins were slightly dilated. Slight anemia was present. The hemoglobin was 63 per cent; the erythrocytes numbered 4,030,000 and the leukocytes 11,000. The urine contained a small amount of albumin, was heavily bile-stained and the sediment contained many erythrocytes. Roentgenograms showed the gallbladder to be filled with stones. The blood urea was normal, 21 and 18 mg. for each 100 c.c. on two occasions, but the serum bilirubin was 12.7 mg. for each 100 c.c. A direct van den Bergh reaction was obtained. There was marked retention of bromsulphalein. A diagnosis of choledocholithiasis with obstruction and biliary cirrhosis was made. Exploration was advised, and was carried out after preoperative preparation.

The surgeon found chronic cholecystitis with stones, and a marked degree of biliary cirrhosis. The common bile duct was partially obstructed by an inflammatory stricture. The stones were removed and cholecystostomy was performed.

The patient did not do well following operation. Only a small amount of

bile drained from the gallbladder. He did not void, and catheterization showed almost complete anuria, the daily output varying between 25 and 80 c.c. Large amounts of glucose and sodium chloride solutions were given intravenously, but without effect on the renal output. The blood urea increased progressively to 190 mg. for each 100 c.c., and the alkali reserve decreased to 36 volumes per cent on the fifth day. The jaundice deepened, with an increase in the serum bilirubin to 18.5 mg. for each 100 c.c.

Because of complete urinary suppression five days after cholecystostomy bilateral renal decapsulation was done as an emergency measure. The kidneys were slightly enlarged, congested, and bile-stained. The operation was without effect, and the patient died about eight hours later.

Swelling and tubular degeneration are the usual renal complications in cases of icterus from any cause. There is little accompanying renal insufficiency in the ordinary case of jaundice, but, as pointed out by Walters and Parham, marked renal insufficiency with the clinical picture of uremia may appear as a postoperative or terminal event. This case well illustrates the postoperative development of renal insufficiency, anuria, and uremia in such a patient. The experimental studies of Bollman, Mann, and Magath have emphasized the rôle of the liver in the formation of urea, and reduction in the content of urea in the blood has been reported in jaundice, especially in cases in which there is acute yellow atrophy of the liver. The development of uremia with elevation of the content of urea in the blood is evidence, however, that urea may form actively even in the presence of marked jaundice and extensive hepatic disturbance.

The sixth and seventh clinical pictures have to do with febrile states in which the liver is playing a certain part. In Case VI the enlargement of the liver led to a form of specific treatment that resulted in recovery despite failure to demonstrate the cause of the fever. In Case VII fever played a striking part in the clinical picture, although its pathogenesis is not clear.

Case VI. Hepatitis (probably amebic).—A man aged forty-nine years first came to the clinic in 1921 because of a papilloma on the right tonsil. The tonsil was removed and found to be benign. He came from the South and had had malaria several years previously. At that time the cecum and ascending colon were palpable and apparently normal. The liver could not be felt. The patient returned in 1923 for examination for the condition of the tonsils. He was in good health at that time. In January, 1925, following an attack of diarrhea, he began to feel run-down and pepless, and was

readily fatigued. This period of malaise was succeeded in February by a series of chills, with a temperature rising at times to 104° F. At first the fever was continuous; later it became remittent. His home physician found him to be very anemic, but did not find evidence of malaria in the blood smear. February 23 the home physician also noted marked enlargement of the liver. There was some tenderness in the right hypochondrium but no jaundice.

The patient returned to the clinic February 28, 1925. At that time he was anemic and somewhat cachectic in appearance. The liver was not palpable, but roentgenograms showed an elevation of the right diaphragm. Various laboratory examinations, such as blood culture, and Wassermann, Widal, and tuberculin tests, were negative. Roentgenograms indicated a lesion in the ileocecal region, and this was explored surgically March 25. An inflammatory lesion of indeterminate nature was found and ileocolostomy was performed. Postoperative recovery was uneventful, and the patient was dismissed in good condition, although he continued to have occasional attacks of low-grade fever. While he was at home he gradually lost weight and strength. The fever recurred. The temperature was normal in the morning but reached 101° to 103° F. in the evening, and he had several mild rigors. The liver again become enlarged and he experienced sharp pain in the epigastrium, along the right costal margin, and over the right scapula and shoulders.

The patient returned to the clinic June 2, 1925. He was pale and cachectic. The abdomen was somewhat distended and the liver was greatly enlarged, reaching from the level of the third rib to that of the iliac crest. The surface was smooth and soft, but it was very tender on pressure. The spleen was not palpable. There was moderate anemia. The hemoglobin was 50 per cent; the erythrocytes numbered 3,660,000 and the leukocytes 11,400. The differential blood count was normal. There was a moderate retention of bromsulphalein and the serum bilirubin was 0.8 mg. for each 100 c.c. Examination of the stool showed the presence of trichomonas, but amœbæ were not found. He was kept under observation in the hospital for several weeks without change in the general condition, but an irregular fever continued. August 28 he was given a course of 50 mg. of emetin hydrochloride twice daily for three days. This was repeated at intervals of two weeks, four courses in all being given. Following this the fever disappeared and he began to gain strength slowly. A month later the improvement was striking. He had gained in weight and strength, the hemoglobin had increased to 60 per cent and the erythrocytes to 4,150,000. The tenderness and pain disappeared from the liver and the liver was reduced considerably in size. When he was dismissed the liver extended from the level of the fourth rib to 2.5 cm. above the umbilicus.

The patient continued to gain weight and strength at his home and was able to resume his normal activities. He returned in May, 1926, for reexamination, when apparently he was entirely well. There was no anemia. The liver was not palpable, tests did not show retention of bromsulphthalein, and the serum bilirubin was 0.3 mg. Another examination in July, 1928, confirmed these data and the apparent completeness of his recovery.

The most interesting feature of this case was the long-continued fever associated with the enlarged tender liver. The majority of the usual etiologic agents capable of causing hepatitis of this type were specifically excluded. Amœbæ could not be demonstrated in the stool. However, the patient's residence in the South, the onset of the illness with diarrhea, and, most significant, the therapeutic response to emetin warranted the diagnosis of diffuse amebic hepatitis.

Case VII. A terminal febrile course in a case of carcinoma of the head of the pancreas with involvement of the liver and obstructive jaundice.—A man aged thirty-four years was admitted to the clinic August 6, 1924 because of painless jaundice of ten weeks' duration. There was a history of a questionable chancre fifteen years before, but the Wassermann reaction was negative. For three months previous to the onset of the jaundice the patient had been drinking excessively. Two days before he noticed that the urine was dark and the stools light. The stools later became clay-colored. He consulted a physician, who gave him three injections of neo-arsphenamine without affecting the jaundice. Bile was obtained by duodenal drainage at that time.

The patient's weight on admission was 116 pounds, representing a loss of 30 pounds in three months, and extreme jaundice was present. There were

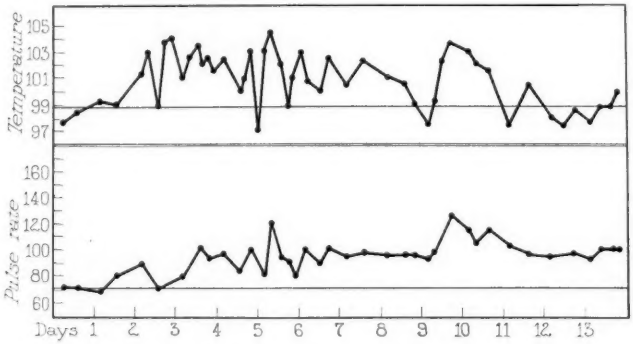

FIG. 224.—Pulse and temperature chart.

no palpable lymph nodes. The edge of the liver was palpable at the level of the umbilicus; the edge was sharp and the surface was smooth. Nodules were not felt. The gallbladder and spleen were not palpable. The urine contained albumin, casts, and bile. The stools were clay-colored and tests for bile were negative. The guaiac test for blood in the stools was occasionally positive. The serum bilirubin was 36.4 mg. for each 100 c.c.,

and there was marked retention of phenoltetrachlorphthalein. Duodenal drainage was attempted on three occasions; there was no return of bile, although traces of blood were obtained.

The patient was kept under observation for ten days, during which time the pulse and temperature were normal. Thereafter the course was strikingly febrile, with repeated chills and a temperature varying between 102° and 104° F. (Fig. 224). The anemia increased rapidly; the hemoglobin fell to 35 per cent. A transfusion was given without benefit. The stools remained acholic, but the serum bilirubin decreased to 16.2 mg. for each 100 c.c., and the jaundice decreased to a corresponding degree. The toxemia, however, increased and during the last week the blood urea became elevated, reaching a level of more than 200 mg. the day before death, September 9. During the last three days of life a mass became palpable below the edge of the liver which was believed to be the gallbladder, but operation was not considered. At necropsy carcinoma of the head of the pancreas, with obstruction of the common bile duct, metastasis to the liver and biliary cirrhosis, were found.

Fever is a common accompaniment of disease of the liver. The low-grade fever associated with abscess of the liver or hepatitis secondary to amebic infection is well known. In such cases the therapeutic use of emetin may effect a striking, and in some cases, a dramatic improvement or cure. Fever may accompany any biliary colic and the association of recurring chills and the hepatic intermittent fever of Charcot in cases of cholangitis, especially in the presence of a ball-valve stone does not need special mention. The terminal rise of temperature sometimes seen in cases of acute yellow atrophy has been mentioned. It may likewise be seen in the end stages of obstructive jaundice from any cause. Thus even in carcinoma of the head of the pancreas where the obstruction occurs from outside the biliary system and infection is to be looked on as minimal, fever may be a striking feature of the latter stages of the clinical course.

The eighth and last picture is one of marked spasmodic or convulsive seizures in case of an elderly physician who had suffered for a long period with disease of the liver.

Case VIII. Hypoglycemia.—A practicing physician aged sixty-six years came to the clinic June 8, 1928, with a long story of cholecystitis and cholelithiasis. He had had cholecystostomy about ten years before because of gallstones. Glycosuria was discovered at that time and he was on a strict

diet for a time, but later stopped it, although traces of sugar were occasionally found in the urine over a period of six years. Following influenza in 1918 he was weak and tired, and never wholly recovered his strength. Slight abdominal distention had been noted several years previously and had since increased progressively. During the last year he had had definite ascites with moderate edema of the ankles. Exhaustion had been much more marked. He had had marked jaundice before the gallbladder was drained. Since then jaundice had been slight, but his complexion never became entirely clear.

Examination disclosed besides the slight jaundice a generalized brownish pigmentation of the skin similar to that so frequently seen in association with biliary cirrhosis. The abdomen was pendulous and contained a moderate amount of free fluid. The liver was enlarged and firm, and extended below the costal margin. The spleen was not palpable. Moderate edema of the ankles was present. Roentgenograms of the region of the gallbladder showed several stones. There was no glycosuria. The serum bilirubin was 2.8 mg. for each 100 c.c., with a direct van den Bergh reaction. The bromsulphthalein test showed moderate retention of dye.

The ascites was readily controlled by diet and the use of merbaphen and euphylline. Because of the roentgenographic evidence of gallstones, and on the specific request of the patient, operation was performed June 27. The surgeons removed a chronically inflamed gallbladder containing many stones. The liver was found to be markedly cirrhotic. The immediate postoperative reaction was satisfactory. Twenty-four hours later he became stuporous, although he was able to answer questions when roused. There was some twitching of the face, with striking, violent, and irregular jerking and twitching of the arms and hands and, to a lesser extent, of the legs and feet. The tremor was somewhat suggestive of that seen in tetany, but the Chvostek and Trousseau signs were negative. The blood sugar was found to be 50 mg. for each 100 c.c. Five hundred cubic centimeters of 2.10 per cent glucose solution was given intravenously, with considerable improvement. The following morning the blood sugar was 122 mg. for each 100 c.c., and thereafter it was normal.

This period of improvement was transitory. The pulse rate and temperature progressively increased. The patient was stuporous, but could be aroused at first. Later, deep coma supervened, although even at this stage there was some restlessness and occasionally slight tremor of the hands. Negativism was present at this time; although he could not be aroused he would actively resist passive movement of the hands or feet. Failure was progressive and he died on the sixth day after the operation.

This case is of particular interest in that there was hepatic insufficiency with hypoglycemia developing twenty-four hours after operation. The hypoglycemia was successfully treated, or at least controlled temporarily, by the administration of glucose, and the terminal picture was the more usual type with stupor.

The clinical picture resembles in many respects that described by Mann in the experimental animal following complete hepatectomy. The development of convulsions following removal of the liver was described years ago by Nolf and his associates. The clinical picture, the presence of hypoglycemia, and its significance in the pathogenesis of the convulsions, and the value of glucose in the temporary control of the convulsions were contributed by Mann and his collaborators. The clinical phenomena attending hypoglycemia are now receiving considerable attention. They were first outlined from the important work with insulin carried on by Banting and his co-workers. Seal Harris recognized the part that hyperinsulin might play in the pathogenesis of hypoglycemia. Concluding proof of hyperinsulinemia was furnished by Wilder, Allan, Power, and Robertson, which has been supported by subsequent studies by Talheimer, Finney, and Finney and Campbell, and Allan.

The clinical factor which I have described here may be due to hypoglycemia. Two suggested cases of hypoglycemia of hepatogenic origin were reported from the clinic by Wetherby and Wilder. Nadler and Wolfer recently reported the occurrence of typical attacks of hypoglycemia in a case of extensive primary carcinoma of the liver. The case reported here, at the time of the patient's death, was regarded as one of spasmodic seizures of the arms and legs of hypoglycemic origin, due, in all probability, to insufficiency of the liver accompanying a mild form of portal and biliary cirrhosis.

Reduction of the fructose and glucose tolerance in experimental obstructive jaundice was found by Snell, Rowntree, and Greene, and by Ferguson. Ravdin reported a reduction in the glycogen content of the liver. Although experimental studies such as these suggest that there probably is some disturbance in the glycogenic function of the liver in all cases of jaundice the variability of the experimental results themselves indicates that the interference is not sufficiently great to be of general clinical significance. Similar variability has been found by those who have used either carbohydrate tolerance tests or the response of the blood sugar to epinephrine as a test of the glycogenic function

of the liver in cases of hepatic disease. Changes undoubtedly take place, but without sufficient regularity to permit much diagnostic import to be assigned to the results in any individual or borderline case. The extent of the hepatic reserve and the adequacy of glycogenesis in most cases is further evidenced by the infrequency with which the hypoglycemic syndrome develops. That it develops so infrequently is fortunate both for the patient and the surgeon. That it develops at all indicates the necessity for careful preoperative preparation of the patient with a diet high in carbohydrate, and the importance of the intravenous administration of glucose both as a preoperative and postoperative measure.

SUMMARY

The cases reported here serve to illustrate the multiplicity of clinical pictures that may be observed in association with hepatic disease. In the eight cases in the present report attention has been directed to: (1) The increasing drowsiness and narcosis closely resembling normal sleep that is a prelude to the development of coma in many cases; (2) the tragic end by sudden and fatal hemorrhage from esophageal varices which may occur even after complete control of ascites by medical measures; (3) the appearance of a group of purpuric spots which may develop after the use of merbaphen; (4) the disorientation and psychic disturbances occasionally observed in patients with severe hepatic disease as a result of, or during, treatment with ammonium salts; (5) the development of toxic nephrosis with renal insufficiency as a terminal or postoperative event in many cases of jaundice; (6) the possibility of amebic infection producing diffuse hepatitis with low-grade intermittent fever as well as solitary or multiple abscesses; (7) the markedly febrile course that may attend obstructive jaundice resulting from carcinoma of the head of the pancreas, and (8) spasmodic or convulsive seizure that may attend hypoglycemia, presumably of hepatogenic origin. It should be emphasized, also, that although the characteristic pictures of each are usually recognizable, several different elements frequently enter into the clinical picture in any one case.

THE COMPLICATIONS AND SEQUELÆ OF PROLONGED OBSTRUCTIVE JAUNDICE

ALBERT M. SNELL, FRANCES R. VANZANT, AND E. STARR JUDD

FEW diseases have been studied with greater thoroughness than those produced by obstructive lesions of the bile passages. Experimental studies and observations on the pathologic physiology of obstructive jaundice are found in the medical literaure of a century ago.[23] At the present time the pathologic changes and the pathologic physiology of obstructive lesions of the common bile duct are still the subjects of intensive study, a fact which attests to the many problems remaining unsolved after a century of effort.

The pathologic changes secondary to obstruction of the common bile duct vary somewhat with the etiologic agent. When the common bile duct is completely occluded as a result of malignant disease, there is enormous dilatation of the intrahepatic and extrahepatic bile passages, which has been described as hydrohepatosis.[7] In the hepatic lesions produced by stone in the common bile duct or by stricture, dilatation of a lesser degree occurs and there is, in addition, a variable degree of infection. The combination of intermittent obstruction and infection produces eventually a form of biliary cirrhosis which may vary greatly in degree and, rarely, may be complicated by subacute atrophy of the hepatic parenchyma. In other cases the overgrowth of connective tissue may occlude the portal system, producing the clinical picture of portal cirrhosis as an added feature. Renal lesions, anemia, peptic ulcers, emaciation, and nutritional defects often complicate the clinical syndrome, and these add greatly to the difficulties of treatment.

Pathologic physiology in obstructive jaundice is well demonstrated in the experimental animal. It consists of: (1) eleva-

tion of the bilirubin and content of bile salts in the blood, the rate of increase depending on the presence or absence of the gallbladder; (2) decrease in the blood urea and nonprotein nitrogen; (3) increase in the blood coagulation time; (4) abnormalities of sugar metabolism, as shown by decreased tolerance to levulose; (5) decreased tolerance to the injection of bile acids, and (6) marked retention of dyes used for tests of hepatic function (bromsulphalein, and so forth).[19] A change has not been observed in the uric acid of the blood; the blood, fats, and lipoids are usually increased, although decreased absorption of fat from the intestine is shown by the hemoconia test of Brule. The blood calcium is usually unchanged except in young animals; in such animals the calcium decreases and there may be skeletal defects suggestive of rickets.[3]

It is significant that all of the foregoing changes can be demonstrated in the human subject, although it is rare that all of them, or even most of them, are observed in any one individual. It is equally significant that reëstablisment of biliary drainage by cholecystenterostomy does not always relieve the situation in the experimental animal or in the human subject. In general it may be said that many of the pathologic and physiologic changes are irreversible. The cases reported here serve as a clinical demonstration of the physiologic and pathologic changes, which follow long-continued obstruction of the common bile duct in the human being, and the difficulties encountered even after the obstruction has been relieved by cholecystenterostomy or biliary fistula. The most serious clinical complications of obstructive jaundice are: (1) hemorrhage; (2) hepatic or renal insufficiency; (3) nutritional defects; (4) anemia, and (5) biliary fistula.

REPORT OF CASES

Case I.—A married woman aged twenty-nine years had experienced severe lumbar pain in December, 1927. At that time a roentgenologic diagnosis of gallstones was made and operation was advised, although other definite subjective signs of cholecystic disease were not present. At operation elsewhere a gallbladder containing stones was removed. Bile began to drain from the wound on the third day postoperatively, and jaundice appeared after permanent closure of the biliary fistula ten months later.

After the appearance of jaundice there was occasional colic followed by deepening of the jaundice; purpura and increasing menstrual bleeding were also noted.

The patient first presented herself at the clinic in April, 1929, one year after the primary operation, with moderate jaundice, secondary anemia and some mild purpuric manifestations. May 1, after one transfusion of blood and 6 gm. of calcium chloride had been given intravenously in divided doses, operation was performed. A benign stricture of the common bile duct was found and choledochostomy was done, leaving in a tube to establish a fistula with the idea of later transplanting the fistulous tract. For four days after operation the patient was practically moribund; bleeding occurred from the gums, nose, mouth, wound, and skin. Daily transfusions finally controlled the bleeding; she made an excellent recovery and was able to return to her home four weeks later.

At the patient's second visit to the clinic, in July, 1929, she was in good condition, having gained about 40 pounds in weight. The fistula was draining a copious amount of bile, averaging about 1,500 c.c. daily, and there was no jaundice. The coagulation time was elevated (twelve and a half minutes) and the serum bilirubin was 2.7 mg. for each 100 c.c. It was decided to wait longer before attempting further surgical procedures.

The fistula closed spontaneously in September, 1929. The patient returned to the clinic immediately, but for several days bile could not be obtained and the jaundice was definitely increased; the serum bilirubin was 4.7 mg. for each 100 c.c. A few days after admission bleeding began from the gums, nose, skin, and uterus, and signs of meningeal irritation appeared which were interpreted as being due to meningeal hemorrhage. The patient was irritable, and manifested extreme photophobia, diplopia, marked opisthotonos and a positive Kernig sign. Her semicomatose state was frequently interrupted by a typical cephalic cry. The pulse was slowed, 44 a minute, the temperature was subnormal, and respirations were only 11 a minute. Lumbar puncture was not successful, yielding only blood; apparently the needle entered a blood clot after penetrating the dura. Repeated transfusions each caused marked temporary improvement. After a time she was well enough to be up in a chair part of the day, but headaches were constant and severe, diplopia was occasionally present, and frequent transfusions had to be given to compensate for gross loss of blood. Meanwhile drainage of bile was reëstablished, but there seemed to be no improvement in the coagulation factors of the blood. The blood platelets, which had been 198,000 when the patient was first examined, now ranged between 40,000 and 94,000. The bleeding time by the usual technic was normal, but wounds in the skin frequently reopened and bled many days after the puncture was made. The prothrombin time was greatly increased. The tourniquet test was slightly positive and the coagulation time varied from twenty to forty minutes; the clot, once it was formed, was normal. Five weeks after the meningeal hemorrhage the patient suddenly became somnolent, and diplopia and severe headaches appeared again. Puncture wounds a week old dribbled blood in a steady stream. The entire body was covered with great areas of ecchymosis. There was hemorrhage from the gums, and blood drained from the biliary fistula con-

tinuously. There were no further signs of cerebral bleeding, except that the pulse rate was slowed. The fundi were normal. The venous blood was practically incoagulable; a fragile clot formed only after two hours and five minutes. Death occurred seven days after the beginning of the second hemorrhagic episode. There was a terminal rise of blood urea due to dehydration. Table 1 gives the data relating to the blood coagulation factors and the effect of treatment.

TABLE 1

SUMMARY OF DATA IN CASE 1

Date.	Blood urea, mg. for each 100 c.c.	Serum bilirubin, mg. for each 100 c.c.	Coagulation time, minutes.	Blood platelets.	Hemoglobin, per cent.	Erythrocytes, millions.	Comment.
3/26		11.5	22	198 000	60	3.68	
4/ 8		13.6	15				After six doses of 0.5 gm. calcium chloride intravenously on successive days.
4/13		15.6	20				Two days after transfusion of 500 c.c. blood; purpura present.
4/19		19.6	13		56	3.60	After a single attack of severe colic.
4/24		15.4	9				After three doses of calcium chloride intravenously on successive days.
5/ 1	24	16.6	20				After three more doses of calcium chloride intravenously on successive days. Choledochostomy for benign stricture of common bile duct.
5/11		13.5			40	2.26	Stormy convalescence with much bleeding; glucose and transfusions daily.
5/20		6.0					Improved; dismissed one week later with draining biliary fistula and slight jaundice.
7/19		2.7	12.5				Returned for observation; condition good.
9/16		4.7	17.5		60	3.86	Drainage from fistula stopped; colic and increasing jaundice.
9/23	18		15				After two transfusions signs of meningeal irritation and generalized purpura.
9/23 to 10/ 2	40	9.2	23	76,000 84,000 83,000	59		Transfusions on alternate days; purpura continuously present; bile drainage profuse.
10/ 2 to 10/18	145		18 to 40	40,000 94,000	67	4.25	Six transfusions; coagulin 20 c.c.; condition slowly improving.
10/22					67	4.08	Purpura increasing; signs of intracranial hemorrhage; gum acacia intravenously.
10/25	111	5.0	37				Purpura increasing; glucose and sodium chloride intravenously.
10/26	73	5.1	125				In extremis; gum acacia, glucose, sodium chloride, and calcium chloride given intravenously; death three days later.

At necropsy there was marked anemia and moderate jaundice of all tissues, with extensive hemorrhages throughout the gastro-intestinal tract,

into the peritoneal cavity, in the substance of the lungs, and in the mucous membrane of the urinary bladder. There was evidence of severe hemorrhages, both old and new, in the dura mater, especially in the posterior cranial fossa, so that the cerebellum was pressed on and appreciably flattened.

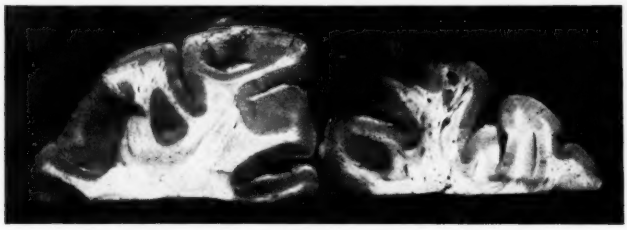

FIG. 225.—Massive and petechial hemorrhages in the frontal lobe.

There were many minute petechiæ throughout the brain and a small subarachnoid hemorrhage at the tip of the frontal lobe (Fig. 225) beneath which were many petechial hemorrhages in the substance of the brain. Figure 226 shows the recent hemorrhages into the dura, old blood pigment and begin-

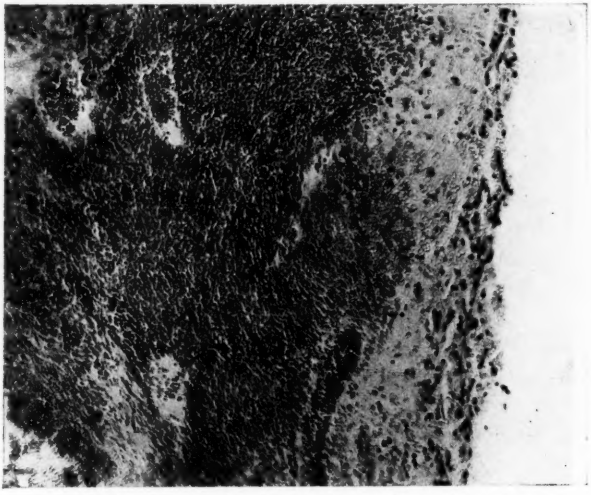

FIG. 226.—Organized and recent hemorrhages in the dura.

ning organization of the clot, just as is seen in the so-called hemorrhagic internal pachymeningitis. The liver was somewhat smaller than normal (1,400 gm.), and microscopic section showed fibrosis in the portal spaces surrounding the

biliary ducts. Figure 227 also shows the presence of bile thrombi and the histologic picture of biliary cirrhosis.

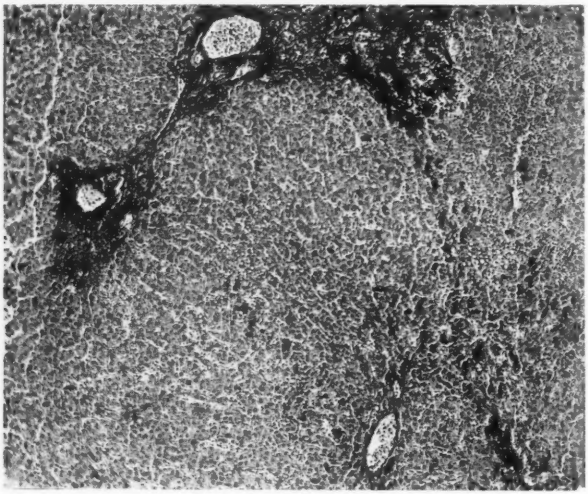

FIG. 227.—Bile thrombi and beginning biliary cirrhosis.

The hemorrhagic diathesis is perhaps the most feared complication of obstructive jaundice, and the one chiefly responsible for the increased surgical risk in this group of patients. In most instances this hemorrhagic tendency makes its presence known only by a prolonged coagulation time and a tendency to slow oozing of blood from incised surfaces. Such cases are usually brought under control by appropriate treatment with calcium chloride and do not present serious difficulty in treatment. In other instances, fortunately not common, there is a far more severe hemorrhagic tendency, which can sometimes be controlled by repeated transfusion of blood. Purpuric spots are not infrequently encountered in this type of case. In extreme examples, such as the case presented, there is not only a prolonged coagulation time and purpuric lesions, but thrombocytopenia and spontaneous bleeding from supposedly intact tissues in every organ of the body. It is in the latter group that extensive hemorrhages in the brain, viscera, skin, and so forth,

are principally encountered. There is no reason to suppose that these groups are distinct entities; they are, rather, varying degrees of the same process.

The cause of this hemorrhagic tendency has been the subject of an enormous amount of clinical and experimental investigation, and a great number of more or less plausible theories have been advanced. Wangensteen recently reviewed the subject and the literature pertaining to it, and those who are interested in the details of the subject are referred to his article. Among the theories which have found favor may be mentioned, first, the idea that the retention of bile or certain of its constituents are responsible for some change in the coagulation mechanism of the blood. Numerous complete studies bearing on this point have failed to substantiate this view since there is no demonstrable correlation between the coagulation time of the blood and the level of bile acids or bilirubin in the blood. Lipoid substances which are known to be retained in the blood in jaundice are not excluded as an etiologic factor, although evidence has not been presented to show that they are in any way responsible. Calcium deficiency does not seem to be responsible,[20] nor is there any constant change in the diffusible fraction of blood calcium in obstructive jaundice which might explain the tendency to bleeding. Fibrinogen is not lacking, as numerous investigators have shown.

Those who have studied the formation of blood clots[6] in obstructive jaundice believe that the difficulty probably lies in the conversion of prothrombin to thrombin, since if thrombin is added in vitro to the almost incoagulable blood of these patients, formation of clot is entirely normal; if prothrombin is added its conversion to thrombin is delayed. Injection of prothrombin solution will not check bleeding in these patients, but has been shown actually to increase the coagulation time. The cause of delay in the formation of thrombin is not known.

The possible effect of the parenchyma of the liver itself on the coagulation of blood has been under consideration since it has been known that injury or destruction of this organ may produce a hemorrhagic tendency. Howell's discovery of the anti-

coagulant, heparin (antiprothrombin), raises the question of possible excess heparin in the blood which acts to prevent the transformation of prothrombin to thrombin. This increase in heparin may be due to excessive production in the presence of injury to the liver or, as has been suggested, to decreased destruction by the liver of heparin formed elsewhere. Since there is no known method for quantitative determination of heparin in the blood, this matter is still sub judice. Mann and Bollman recently showed that after hepatectomy antithrombin may be either increased or decreased, and they noted that after removal of the liver the blood occasionally at first may be incoagulable, and later may coagulate normally.

The variety of measures advocated for the relief of the hemorrhagic tendency in jaundice is evidence in itself of the lack of specificity of any of the measures. Relief of the underlying condition is the first consideration. When possible, operative measures to relieve biliary obstruction should be instituted as promptly as possible after preoperative preparation. Walters has shown conclusively the beneficial results to be obtained in many cases by the intravenous administration of calcium chloride, as well as the lowering of the general operative mortality in jaundiced patients by using this treatment as a routine. Parathormone has been used, but does not significantly affect the coagulation time.[27] Transfusion is probably the most valuable single measure employed in the resistant case. Various hemostatic substances, including platelet extracts have had their advocates, but, on the whole, all are inferior to transfusion of whole or citrated blood. Bollman has used intramuscular injections of the subject's own blood in dosages of 20 to 30 c.c., with success in his experimental animals. This treatment has been used in clinical cases with some success.

Irradiation of the spleen has been advocated recently. Stephen found a decrease in coagulation time even in normal individuals following this procedure; he attributed this to the rapid breakdown of large numbers of lymphocytes and leukocytes. Neuffer used this method successfully to control bleeding in hemophilia. Jurasz reported that such treatment was par-

ticularly valuable as preoperative preparation in jaundiced patients; he found a decrease in coagulation time for twenty-four hours or longer after irradiation. Our experience with this form of treatment is not sufficient to warrant an opinion as to its value, but it deserves further trial in selected cases. Often cycles of bleeding can be observed, especially if a determination of the coagulation time is made daily or every other day. It is well to take advantage of this natural variation in choosing the time for necessary surgical procedures; it is equally necessary to consider these spontaneous variations in evaluating the results of treatment.

The unusual severity of the hemorrhagic tendency and the failure of all therapeutic measures in Case I may perhaps be explained on the basis of thrombocytopenia. This is an uncommon observation and may be regarded as due to the toxic effect of the jaundice on the bone marrow. There were no other signs of essential thrombocytopenic purpura; clot retraction took place in ninety minutes; the tourniquet test was only faintly positive, and the bleeding time was not prolonged. Apparently platelet deficiencies must be considered as a possible complication in certain severe types of the hemorrhagic diathesis of obstructive jaundice.

Case II.—A woman aged forty-two years was operated on elsewhere in November, 1928, after having suffered from recurring attacks of gallbladder colic over a period of eight years. Stones were not found in the gallbladder, which was reported to show the changes of cholesterosis; cholecystectomy and appendectomy were done. Drainage of bile from the wound began almost immediately. A second operation was performed two weeks later; a fibrous stricture of the common bile duct was found, but the continuity of the duct could not be reëstablished. A second attempt to repair the stricture was made five weeks later, but the operation had to be stopped on account of the poor condition of the patient. Convalescence was prolonged, but at the end of six months she was well enough to be up part of the day. Infrequently the fistula closed for a few days, thereby increasing jaundice and often provoking fever; reopening of the fistula always relieved the symptoms. There had never at any time been the slightest tinge of bile in the stools and she had never been entirely free from some degree of jaundice. One week before the patient came to the clinic in September, 1929, daily chills and high fever, marked prostration and extreme shortness of breath had developed.

At the time of admission marked pallor, edema of the eyelids, an icteric

tinge to the sclerotics and multiple purpuric spots were noted. The purpuric spots were especially numerous over the lower extremities. She was dyspneic even while lying quietly in bed. The heart and lungs appeared normal. The liver was slightly enlarged, but the spleen was not palpable. A fistulous opening in the right upper part of the abdomen was draining clear dark brown bile. The urine was normal; the hemoglobin was 15 per cent; erythrocytes numbered 2,230,000, and the leukocytes 15,000. The blood urea was 161 mg. for each 100 c.c. The coagulation time by the Lee-White method was twenty-six minutes. The van den Bergh reaction was direct with a serum bilirubin of 5.1 mg. for each 100 c.c. A blood culture showed colon bacilli.

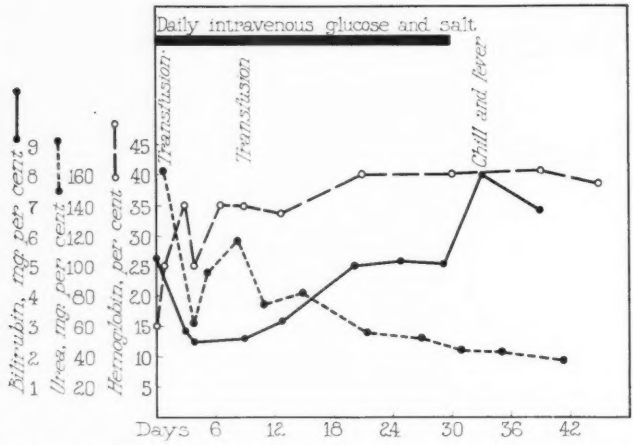

FIG. 228.—Curves of blood urea, hemoglobin, and bilirubin as affected by treatment.

A transfusion of 500 c.c. of citrated blood was given immediately, and a second transfusion was given five days later. One liter of 10 per cent glucose with 1 per cent sodium chloride solution was also given intravenously daily, usually with the addition of 0.5 mg. of calcium chloride. Under this treatment steady improvement occurred. After a few days culture of the blood was negative; there was rarely any fever or chill and then apparently only as a result of the intravenous injections. The hemoglobin rose to 40 per cent, the blood urea fell to 41 mg. for each 100 c.c., and the coagulation time to thirteen minutes, but the serum bilirubin remained at a level of about 5.1 mg. for each 100 c.c. Because there had been some question of slight jaundice prior to operation the possibility of hemolytic icterus arose; however, the fragility of the erythrocytes was normal. Analysis of the mineral constituents of the blood showed values at the lower limits of normal. Calcium was 8.40 mg., the potassium 14.43 mg., magnesium 2.79 mg., sodium 303 mg., and chlorides 600 mg. for each 100 c.c.

The diagnosis was stricture of the common bile duct, complete external biliary fistula with biliary cirrhosis, toxic nephrosis, severe secondary anemia, and infection of the blood from colon bacillus which was probably terminal in nature. The patient's recovery from the septicemia and the nephrosis was phenomenal. Figure 228 shows the progress of the case as reflected by the blood urea, hemoglobin, and serum bilirubin. With the knowledge in mind that the patient had often had trouble with the fistula closing temporarily before she came under our care, and also remembering that dogs with fistula do not do well unless special care is taken to keep the fistula clean and draining continuously, we devised an arrangement for applying gentle suction to the fistula by means of a small electric pump. This suction was maintained for six to eight hours once or twice a week and served to maintain free drainage of bile.

In spite of the patient's improved condition, she consistently lost weight at the rate of 2 or 3 pounds a week; her weight reached the low level of 84 pounds. Anorexia and vomiting were in large part responsible. We resorted finally to returning to her, by means of a stomach tube, all of the bile draining from the fistula. Prompt subsidence of vomiting and noticeable increase in appetite followed the institution of this measure. Although she did not gain weight she felt stronger and the daily output of bile increased. If the condition continues to improve, operation may eventually be attempted, but at the present time the operative risk is almost prohibitive.*

For many years the complete loss of bile from the body was considered innocuous, but a constantly increasing number of observations is being reported, showing that nutritional disturbances are likely to ensue whenever all the bile is diverted from the intestinal tract. Mayo-Robson cited a case of external biliary fistula of fifteen months' duration without loss of weight or strength. Bernays reported a case in which the patient survived in good health for eleven years with a complete fistula.

* The patient returned to the clinic considerably improved in general health, but still moderately jaundiced and anemic. She stated that the fistula had closed frequently and that she had had fever, chills, and increase in jaundice at these times. The serum bilirubin averaged about 10 mg. for each 100 c.c. and the blood urea was at a normal level. The hemoglobin was 40 per cent (Dare). It was thought advisable to explore the fistula to secure better drainage; this was done January 31, 1930. The liver was bound in adhesions and was the site of extensive suppurative hepatitis. Satisfactory exploration was impossible, but part of the fistulous tract was dissected out and a tube was placed in the common duct with the hope of establishing a new fistula. The right lobe of the liver was punctured in several places and from the openings bile and pus escaped. Convalescence has been uneventful thus far, and there has been a free drainage of bile and pus from the wound, with a definite decrease in the degree of jaundice.

On the other hand, experimental work with dogs does not support the view that bile is an entirely excretory substance. Hooper and Whipple reported their experience with dogs with bile fistula, and stated that extreme care must be taken with the diets if the dogs are to be kept in good condition, although the inclusion of small amounts of bile given with food made dietary precautions unnecessary. Recent work by Tammann seems to establish the fact that simple loss of all of the bile from the intestinal tract for more than six months affects the nutrition of experimental animals so that progressive weakness ensues, with the development of extreme grades of osteoporosis.

Failure to absorb fat in the absence of the bile acids was first thought to be responsible for the loss of weight, and certainly there seems to be an increase in the fat content of acholic stools. There is evidence that with loss of fat there is consequent loss of fat-soluble vitamines, and also that calcium is not absorbed, owing to the formation of insoluble calcium soaps which are lost in the feces. If even a small amount of bile finds its way into the intestine, nutrition may be maintained at a normal level. Feeding bile theoretically should be almost as valuable as the establishment of an internal biliary fistula so far as nutrition is concerned, but Tammann has not found this to be the case, although his dogs improve if they are fed bile. Other observers have stated, however, that a dog will keep in good condition if he is simply allowed to lick his fistula, thereby taking into his stomach a portion of the bile excreted. Whipple's dogs did well if fed even small amounts of their own bile; ox bile could not be substituted for dog bile with the same results. Ross and McGee also noted improvement in their patients who were taking their own bile and they likewise found an increase in the production of bile.

Wangensteen recently reported two cases of external biliary fistula in which there was great loss in weight and strength, and commented fully on the nature and significance of the ensuing nutritional defect. The low levels of the blood minerals in our patients are of interest in connection with the previously mentioned studies on the osteoporosis which follows biliary

fistula in animals. The nature of the dietary deficiency in these cases is not clear; the loss of fat is perhaps of first importance, but the hepatic injury secondary to infection and the dilatation of the bile passages may likewise interfere with the assimilation of protein and carbohydrate, as the following case will show.

Case III.—A married woman aged thirty years came to the clinic in June, 1929, with a history of recurring gallbladder colic over a period of nine years, beginning during the latter half of her first pregnancy. Ten weeks after the birth of a second child, in March, 1927, she had experienced a prolonged severe attack of upper abdominal pain; at operation elsewhere a gangrenous gallbladder containing forty stones was removed. One stone was likewise removed from the common bile duct; a biliary fistula resulted, which drained seven weeks before closing. After a tedious convalescence recovery apparently was complete. Seven months after the operation she had another attack of severe colic; this was followed shortly by jaundice, which had been present for about a year at the time of her registration at the clinic.

The patient's extreme emaciation was striking. She weighed 98 pounds as compared to her previous weight of 200 pounds. Jaundice was moderate; the serum bilirubin being 5.2 mg. for each 100 c.c. The coagulation time was nine minutes. A diagnosis of obstructive jaundice, probably due to stricture of the common bile duct, was made. At operation a remnant of the duct was found in a mass of scar tissue and this remnant was reconstructed over a T-tube. Marked biliary cirrhosis was noted at the operation, and also definite splenic enlargement. Convalescence was uneventful, but two weeks later cycles of fever developed lasting five to eight days, accompanied by hematuria, generalized purpura, and bleeding from venipuncture wounds. These periods alternated with periods of similar length during which there was no bleeding, and the patient felt fairly well. She continued to lose weight and the jaundice became deeper; the serum bilirubin increasing to 20 mg. for each 100 c.c. The liver became greatly enlarged, and the spleen was palpable at the level of the umbilicus. The stools contained bile, and a free flow of bile could also be obtained on duodenal drainage. The hemoglobin remained at 45 per cent, the blood platelets averaged 124,000, and the coagulation time varied from eighteen to twenty-six minutes. The blood urea ranged from 6 to 12 mg. for each 100 c.c.

The T-tube was removed at this time without increasing the jaundice, and the stools continued to show the presence of bile. It seemed evident that the jaundice was due to biliary cirrhosis and hepatic insufficiency. Transfusions were used to control the episodes of bleeding since all other measures seemingly had no influence. No form of treatment seemed effective in improving the patient's general nutrition. An adequate diet, which was low in protein and high in vitamine-containing foods and which included yeast, was given, but the weight remained stationary. The nutritional defect was studied to determine whether the condition resembled in any way that seen after an Eck fistula or partial hepatectomy.

The patient finally improved sufficiently to return to her home, but her weight did not increase and there was no appreciable gain in strength. A definite cyclic hemorrhagic tendency is still present.

Case III is presented because of the presence of two complicating factors: a hemorrhagic diathesis and nutritional defects of marked severity. The nature and significance of the hemorrhagic tendency in such cases has been considered. It will be noted that in this patient there was no reduction in the blood platelets, although the bleeding from punctures in the skin was fully as difficult to control as in Case I. There was also a tendency for the bleeding to occur in cycles, a point which has been mentioned.

The nutritional defects in Case III cannot be explained on the basis of exclusion of bile from the intestinal tract, since the stools contained quantities of bile throughout the patient's stay in the hospital. They represent, rather, an effect produced by injury to the hepatic parenchyma and, therefore, interference with one of the great metabolic laboratories of the body. The major defect probably lies chiefly in the assimilation of carbohydrate. The part played by the liver in carbohydrate metabolism is too well known to require further comment. Ravdin recently reviewed the effect of obstructive jaundice on the glycogenic function of the liver and the hepatic glycogen reserve. He has brought forward good evidence to show that the assimilation of carbohydrate may be decreased in advanced hepatic disease.

The effects of total hepatectomy on the metabolism of protein substances are of interest in connection with the metabolic disorders known to be associated with hepatic disease. As Mann and his associates have shown, there is a rapid fall in the concentration of urea in the blood, urine, and tissues after the removal of the liver, indicating that urea has ceased to form. There is also an accumulation of amino nitrogen in the blood, urine, and body tissues which is of rather small magnitude because of the absorption of amino acids by the muscles. The uric acid content of the tissues and body fluids also rises, and there is reduced tolerance to the injection of uric acid. The

ammonia content of blood increases as well, and the urinary output of ammonia shows a relative increase with a fall in the absolute value after a few hours.

Reduction in the amount of functioning hepatic tissue by an Eck fistula or partial hepatectomy does not, however, produce changes of the same degree. There may be a fall in the percentage of excretion of urea from the urine, but this reduction is due chiefly to increased excretion of ammonia. Partially hepatectomized animals show intolerance to the injection of ammonia, amino acids, and uric acid, indicating that the reserve function of the organism is greatly reduced so far as protein metabolism is concerned. In animals with experimental obstructive jaundice there is usually a fall in the blood urea and nonprotein nitrogen, but otherwise signs of defective protein metabolism cannot be demonstrated.

In the human subject one can rarely demonstrate any striking abnormalities of protein metabolism even in advanced hepatic disease. In obstructive jaundice of long duration low blood urea values are not infrequently encountered, but the significance of this observation is, of course, debatable. The partition of nitrogen in the urine has been studied by Rowntree, Marshall, and Chesney; the percentage of urea nitrogen in the urine was less than normal, and the ammonia and amino-acid nitrogen in the urine were increased in a majority of their cases. We were recently struck by the low levels of blood urea in a group of patients with prolonged obstructive jaundice (including Case III), and we repeated the urinary partition studies previously mentioned in order to determine whether any abnormality in protein metabolism could be demonstrated. The results were within normal limits except in this particular case, which incidentally showed the most marked weight loss and muscular wasting of any in the group (Table 2, page 1432).

It will be noted that the principal change shown by figures in Table 2 is a decrease in the formation of urea, manifested by low figures for both blood and urine. These figures returned to normal as the condition of the patient improved. Since urea is derived chiefly from ammonia, which is also excreted as a waste

TABLE 2

SUMMARY OF DATA IN CASE 3

Date.	Calculated nitrogen intake, gm. for each day.	Blood.		Urine.						
				Total nitrogen, gm.	Urea nitrogen.		Ammonia nitrogen.		Amino-acid nitrogen.	
		Urea, mg. for each 100 c.c.	Amino acid, mg. for each 100 c.c.		Total, gm.	Per cent of total nitrogen.	Total, gm.	Per cent of total nitrogen.	Total, gm.	Per cent of total nitrogen.
9/ 8	12.8			6.9	4.77	69.0	0.63	9.1	0.101	1.5
9/ 9	7.7			8.1	5.41	66.7	0.41	5.1		
9/10	9.1	12	6.9	12.5	7.2	57.5	0.7	5.6		
9/23	7.2	12		5.3	3.51	66.2	0.44	8.1	0.156	2.9
9/24	4.9			6.7	4.8	71.5	0.58	8.6	0.144	2.1
10/ 3	11.0	12		6.49	5.13	79.0				
				5 to 10		70 to 80		8.0		1.8 to 2.7
Normal.				10		80 to 85		5.0		1.8 to 3.5

product, it is evident that no great harm can come to the organism from this defect so long as adequate urinary excretion is maintained. Loss of amino-acid nitrogen would be of considerably more significance, and there is evidence that this is taking place on at least two of the test days. If one subtracts the urea nitrogen and ammonia nitrogen from the total urinary nitrogen, the remaining nitrogen (a mixture of amino acid, uric acid, creatinine, creatine, and undetermined nitrogen) averages about 1.5 gm. in a normal person (8 to 15 per cent of the total urinary nitrogen). In this patient normal figures for this fraction were obtained on four of the six test days. On two consecutive days (September 9th and 10th) the values were high, 2.3 gm. and 4.6 gm., respectively. This rise was undoubtedly due to the fact that the intake of protein was deliberately increased as a sort of tolerance test. It is evident from the foregoing figures that there is a definite failure to metabolize more than minimal amounts of protein in certain advanced cases of hepatic disease. Although this is rare, it is undoubtedly of considerable significance when it does occur. In Case III there was clinical evidence

of intolerance to a high intake of protein, in the form of headache, nausea, anorexia, and so forth, when the diet was increased. Curiously enough, the serum proteins were found to be low and there was definite edema of the extremities during the latter part of the patient's stay in the hospital, reminiscent of nutritional edema which is produced by starvation and low intake of protein.

There is one other clinical phenomenon which has been called to our attention. In patients with hepatic disease it has been noted[10] that blood from a fasting donor produces little, if any, toxic effect, and that blood from a donor in the postabsorptive state will almost invariably cause a severe reaction. This can hardly be explained on any basis except that there is a marked intolerance to the blood-borne end-products of protein metabolism in patients with advanced hepatic injury.

Case IV.—A woman aged forty years came to the clinic in February, 1928. Eight years previously she had had abdominal pain and persistent jaundice, and repeated attacks of upper abdominal colic over a period of a year, with qualitative food distress in the intervals. Six years of relief followed, at the end of which time she again had frequent attacks, occasionally associated with jaundice. At operation elsewhere, in March, 1927, the gallbladder, which contained stones, was removed. Jaundice was present immediately after the operation. In June of the same year, a biliary fistula was established spontaneously, but the jaundice never completely cleared even while bile drained copiously from the fistula.

At the time of the patient's examination, she was moderately jaundiced. The biliary fistula had closed; the stools were clay colored. There was definite tenderness throughout the upper part of the abdomen. Laboratory data were essentially negative except for the presence of bile in the urine, slight secondary anemia and serum bilirubin of 7.7 mg. for each 100 c.c., with a direct van den Bergh reaction. The coagulation time of the blood was normal. A roentgenogram of the thorax showed elevation of the diaphragm on the right. A diagnosis of obstruction of the common bile duct due to either stone or stricture was made, and exploration was advised.

Marked stricture of the hepatic duct was found, and hepaticogastrostomy was performed over a catheter. After the operation the jaundice cleared, the serum bilirubin fell to 1.6 mg. for each 100 c.c. Two months later, colics, fever, and jaundice again appeared and a second reconstruction of the common bile duct was attempted; serious difficulties were encountered, but finally a free flow of bile was obtained from the surface of the liver, and the first portion of the duodenum was sutured over this region. This operative procedure was more successful, and the patient remained well until August, 1929, except for an occasional mild colic and chill. At this time, after the

extraction of three infected teeth, a septic type of temperature developed, with daily chills, drenching sweats, a hacking nonproductive cough, and soreness through the right side of the thorax. The patient returned to the clinic six weeks later.

On examination the right lower part of the thorax was definitely dull and roentgenograms showed marked elevation of the diaphragm on the right. A diagnosis of subdiaphragmatic abscess was made and aspiration was attempted without success. A few days later the abscess perforated into a bronchus. The patient barely survived the shock of this and the conse-

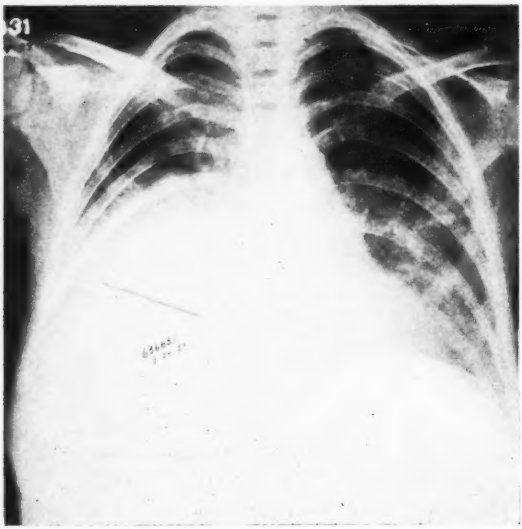

FIG. 229.—Roentgenogram of the chest showing elevation of the diaphragm with air bubble in subdiaphragmatic abscess. Pneumonia involving the base of the right lung.

quent pneumonia. For four days she was in extremis; weakness and prostration were extreme, the pulse rate was rapid, and the temperature was subnormal. Cyanosis developed whenever it was necessary to take her out of the oxygen tent in which she had been placed. Finally the temperature rose to 103° F. and concomitantly she seemed stronger; from this time slow but continuous improvement was noted. There was a daily elevation of temperature and persistent cough, with expectoration of several ounces of foul pus, which usually was greenish-yellow, but occasionally had the typical appearance of pus from a liver abscess. Bile was not demonstrated in the expectorated material. A course of emetin was given without perceptibly influencing the course of the illness.

Aspiration of the subdiaphragmatic region was attempted again when the patient's progress seemed to have reached a standstill five weeks after the formation of the bronchial fistula. Pus could not be obtained, but a large accumulation of clear bile was removed. The surgeon stated that it seemed impossible to obtain such an amount of bile unless there was an extrahepatic bile pocket beneath the diaphragm. Following this procedure improvement was striking; the temperature fell to normal, with an appreciable gain in the patient's weight and strength. Four weeks after the aspiration, the patient returned to her home; the bronchial fistula apparently was closed and her general condition excellent in every way, except that very slight jaundice still remained; the serum bilirubin was 4.4 mg. for each 100 c.c.

The condition of the thorax was observed by means of roentgen-ray examinations at approximately weekly intervals. The roentgenograms first showed simple elevation of the diaphragm on the right, and later showed bilateral pneumonia, chiefly involving the lower lobes. The fistulous tract became apparent as the surrounding pneumonia cleared, and an air bubble below the diaphragm marked the site of perforation (Fig. 229). Pneumothorax did not develop at any time. As the fistula closed, the air bubble disappeared, but the diaphragm remained elevated on the right and pleural thickening persisted.

This case closely resembles a case of bronchobiliary fistula reported by Morton and Phillips, in which a subdiaphragmatic abscess ruptured through a bronchus ten months after cholecystostomy for stones. In their recent article on bronchobiliary fistula they stated that bile must be present in the sputum in order to establish this diagnosis. This was not true in our case, although the sputum strongly suggested a hepatic origin, and the finding of an extrahepatic pocket of bile seemed to corroborate this view. These authors stated that echinococcus cysts of the liver and amebic abscess are the commonest etiologic factors in this condition; other cases are secondary to nonspecific infection of the liver or bile passages. We cannot be dogmatic in denying the possibility of metastatic abscess from a periapical focus in our case inasmuch as the symptoms developed a few days after extraction of three teeth, but in view of the previously demonstrated elevation of the diaphragm this seems rather unlikely. In cases of stricture or stone of the common bile duct, it seems probable that multiple small abscesses of the liver do occur in the substance of the liver secondary to dilatation and infection of the biliary radicles. Should these areas enlarge or coalesce, an extrahepatic collection of pus

and bile might easily perforate to form a hepaticobronchial fistula.

Hepatic or subdiaphragmatic abscesses seem to be an extremely rare complication of obstructive jaundice. This is the only instance which has occurred at The Mayo Clinic in a rather large series of cases with biliary infection. Treatment of these cases is a problem. Although adequate drainage of all accumulations of pus is a principle of surgery, this patient was at no time in a condition to tolerate radial surgical treatment. Although rupture of the abscess through a bronchus furnished inadequate drainage, it seemed inadvisable to attempt to provide anything more extensive at the time. The end-result in this case has so far fully justified the conservative measures employed in treatment, although further operative procedures may be necessary at some future date.

SUMMARY

The cases presented illustrate the serious complication and sequelæ which attend prolonged obstruction of the bile passages. It will be noted that in all of the cases strictures of the common or hepatic bile ducts had developed following previous operations on the gallbladder; the infection and dilatation of the intrahepatic bile passages, which occur in this condition, have been mentioned. Chronic intermittent obstruction from stone in the common bile duct may produce an identical clinical picture. These cases emphasize the importance of early surgical treatment in cholecystic disease, as well as the care which must be taken to insure the patency of the bile passages at the conclusion of such operations. Prompt recognition and early treatment of obstruction of the common bile duct when it does occur will obviate most of these serious complications; the hepatic injury occasioned by such obstruction is frequently, if not always, irreparable if relief is too long delayed.

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CLINICAL CONSIDERATION OF SOME TYPES OF INTRAHEPATIC JAUNDICE

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INTRAHEPATIC jaundice arises from a variety of factors. The etiologic agent in many cases is infection, such as catarrhal jaundice, Weil's disease, yellow fever, typhoid, or pneumonia. Hepatic lesions with icterus occur from various chemical poisons, such as chloroform, phosphorus, alcohol, and "aëroplane dope." In more recent years arsenical and cinchophen products have assumed a more prominent rôle, and Cases I and II reported here are illustrative of such conditions. Intrahepatic jaundice also occurs in chronic passive congestion of the liver, and in degenerative conditions from endogenous intoxication such as hyperthyroidism. There is also a large group of cases in which the etiology is unknown. Many cases of portal cirrhosis, non-obstructive biliary cirrhosis, and acute and subacute yellow atrophy belong in this category. Finally, jaundice of this type may occur at certain stages of some cases of obstruction in the biliary tract (Case III). In other cases differential diagnosis may be extremely difficult; Case IV is illustrative of these problems.

REPORT OF CASES

Case I.—A woman aged fifty-seven years came to the clinic July 8, 1929, because of jaundice of eleven days' duration. Five years previously she had been to the clinic because of moderate benign hypertension; at that time the systolic blood pressure was 200 and the diastolic 120. In more recent years she had complained of occasional pains in the shoulders, elbows, and other large joints. In February, 1929, the joints of both hands had become painful and swollen, and there had also been some pain in both shoulders and elbows. The patient had consulted a physician who prescribed capsules. After she had taken nine of these capsules she began to have generalized pruritus, which disappeared when medication was discontinued. In April, 1929, she was given powders, and she again had itching after taking only one

powder; again medication was discontinued. About the latter part of May her physician prescribed oxyliodide tablets, two to be taken after each meal and at bedtime. After she had taken two tablets she began to itch, and treatment was discontinued for a week. She was advised by her physician to continue taking the tablets and to try to control the pruritus by means of soda baths. Anorexia then developed, and she lost 10 to 15 pounds in weight. Eleven days before admission she became jaundiced. The tablets had been discontinued two days before the onset of jaundice. With the onset of jaundice the arthritic pains lessened. Jaundice became progressively deeper, and associated with it were moderate pruritus and acholic stools. There was no nausea, vomiting, chills or fever prior to her admission to the hospital.

On examination the patient was deeply jaundiced and showed some evidence of loss of weight. The systolic blood pressure was 130, and the diastolic 80. There was slight swelling and pain on movement of the joints of both hands. Examination of the abdomen was negative. Urinalysis was negative except for the presence of bile. The hemoglobin was 70 per cent; erythrocytes numbered 4,240,000, and the leukocytes 10,400. The Wassermann reaction of the blood was negative. The blood urea was 9 mg., and the blood sugar was 54 mg. for each 100 c.c. The readings for serum bilirubin varied from 30.4 to 44.4 mg. for each 100 c.c. The blood coagulation time (Lee and White) was within normal limits. The blood platelets were 88,000 for each cubic millimeter. Duodenal drainage yielded small amounts of clear amber bile.

July 24, 1929, the patient became semicomatose, irrational, and had urinary incontinence. For one or two days previously she had complained of nausea and some vomiting. There was evidence of subcutaneous hemorrhages. July 26, she was deeply comatose and a temperature of 102° F. developed. The intravenous administration of solutions of glucose and sodium chloride was of no avail. She died July 26, 1929. Necropsy revealed subacute yellow atrophy of the liver and numerous hemorrhages throughout the body.

The outstanding features of this case were the persistent, deep, painless jaundice, with subsequent anorexia, nausea, vomiting, asthenia, and coma following the continued use of oxyliodide. The case is illustrative of the toxic effects of one of the newer drugs that are being used in the treatment of arthritis and various neuromuscular pains, namely, cinchophen and its derivatives. In a rather high percentage of our cases of intrahepatic jaundice there have been previous neuromuscular pains. An increasing number of cases are appearing in the literature in which severe toxic jaundice has developed, not infrequently with a fatal outcome, as in this case. Anderson and Teter have reviewed the literature on the subject briefly. In Case I gen-

eralized pruritus developed when the patient was first given the oxyliodide, and it subsided on its discontinuance, only to reappear when it was again administered. In the use of arsenical preparations in the treatment of syphilis, such a symptom is indicative of intolerance, and such treatment should be discontinued or used with extreme care. Similarly we believe that, with the use of cinchophen, the development of pruritus should be a warning to the physician to discontinue its use. We have seen several cases which presented this warning.

Continuation of the jaundice without any evidence of decline, early onset of anorexia, extreme nausea, and vomiting were indicative of serious hepatic injury, and indicated a serious prognosis. Profound asthenia, drowsiness, and finally coma ensued.

Case II.—A woman aged forty-three years, a bookkeeper, came to the clinic October 17, 1928, complaining of weakness, pruritus, generalized pigmentation of the skin, and attacks of upper abdominal pain. Enlargement of the thyroid gland had existed since she was twelve years of age, and for many years she had had attacks of tachycardia, palpitation, slight dyspnea, and intolerance to heat. For about eighteen months prior to admission she had had generalized pruritus, and for the last two months she had complained of attacks of upper abdominal cramp-like pain accompanied by nausea and slight vomiting.

On examination the patient appeared well nourished and had a generalized "rain-drop" pigmentation of the skin. There was no keratosis of the palms or soles. The systolic blood pressure was 180, and the diastolic 115. There were large adenomas of both lobes of the thyroid gland. Slight tenderness was noted over the region of the gallbladder. The specific gravity of the urine was 1.015, and it contained a slight trace of albumin. The hemoglobin was 70 per cent; the erythrocytes numbered 4,160,000, and the leukocytes 8,300. The Wassermann reaction of the blood was negative. Examination of the urine for arsenic was negative, but after biopsy of the skin the presence of crystals of arsenic was revealed by Osborne's stain. The basal metabolic rate was +10 per cent. A test of hepatic function showed retention of dye graded 4. The serum bilirubin was 3.4 mg. for each 100 c.c., and the van den Bergh reaction was direct. The blood urea was 22 mg., and the blood sugar 100 mg. for each 100 c.c. A cholecystogram revealed a nonfunctioning gallbladder with multiple stones.

October 10, 1928, subtotal thyroidectomy was done. October 27, abdominal exploration revealed the liver to be congested and full of little cystic, granular eminences which bled when touched; the spleen was twice normal size and its consistence on palpation appeared similar to that of the liver. The gallbladder contained multiple stones and there were two stones in the

cystic duct. The pancreas, stomach, and duodenum were normal. The gallbladder was opened, and the stones were removed. The patient was dismissed from the hospital November 25.

The patient returned, April 18, 1929, for reëxamination. Her chief symptoms were continuation of the pruritus and pain in the right upper quadrant of the abdomen almost continuously since operation. The arsenical pigmentation of the skin was still present and there was considerable tenderness over the right upper part of the abdomen. There was a moderate amount of ascites. The edge of the liver was palpable 3 cm. below the right costal margin, but the spleen could not be felt. Arsenic was found in the urine. The hemoglobin was 70 per cent; the erythrocytes numbered 4,150,000 and the leukocytes 5,700. The serum bilirubin varied between 2.8 and 5 mg. for each 100 c.c., and the van den Bergh reaction was direct. A test of hepatic function showed retention of dye graded 4. Duodenal drainage was done several times, and each time a free flow of amber-colored bile was obtained. A glucose-tolerance test revealed a normal response. The blood sugar was 87 mg., and the blood urea 17 mg. for each 100 c.c. Treatment consisted of ammonium nitrate and a diet restricted in salts and fluids in order to diminish the ascites and prevent reaccumulation of fluid in the tissues.

The patient returned, September 17. She stated that she had been in fair health until August, when she had begun to have a series of "weak spells" with dizziness. Two weeks later she began to vomit large amounts of blood, and this was repeated four times within a week. Following each hemorrhage the stools were black. The abdomen had increased rapidly in size since the hemorrhages, and she also complained of attacks of cramps in the arms, forearms, thighs, and legs; each attack lasted about five minutes. While in the hospital she had vomited a large quantity of blood.

The patient was anemic and had considerable ascites. The hemoglobin was 31 per cent; the erythrocytes numbered 2,060,000 and the leukocytes 6,100. The blood urea was 26 mg., and the blood sugar 97 mg. for each 100 c.c. The serum bilirubin was 1.1 mg. for each 100 c.c., and the van den Bergh reaction was direct. Abdominal paracentesis was done September 24, 1929, and 3,600 c.c. of clear, straw-colored fluid was removed. A transfusion was also given, and the hemoglobin rose to 43 per cent. Further treatment consisted of a diet low in salt and fluid, and ammonium nitrate and salyrgan intravenously. The patient left the hospital, October 12, 1929.

In this case three factors must be considered from the causative standpoint, the cholecystitis, the adenomatous thyroid gland, and the chronic poisoning from arsenic. The occurrence of ascites in obstructive jaundice is rare. Rolleston stated that it is a general opinion that mechanical obstruction seldom, if ever, causes genuine cirrhosis, even though gallstones occur slightly more frequently in cases with cirrhosis than in cases without cirrhosis. Cases are occasionally encountered in which

prolonged obstruction of the common bile duct is complicated by ascites due to a cirrhotic process. However, we have encountered an occasional case of cirrhosis with portal obstruction and choledocholithiasis in which these conditions were apparently independent pathologic processes. In Case II we believe that the gallstones were coincidental.

Hyperthyroidism, especially of the more severe and prolonged types, is not infrequently accompanied by degenerative conditions of the liver. However, in this case there was no evidence at this time of hyperfunctioning of the thyroid gland.

The ability of arsenic to produce hepatic injury has long been recognized. Since the advent of the use of arsphenamine and other organic arsenical compounds in the treatment of syphilis, there has been an increase in the prevalence of jaundice, and it is difficult to escape the conviction that arsenic has been a significant factor. Although in this case a history of the therapeutic use of arsenic could not be obtained, the dermatologic picture was characteristic and arsenic was demonstrated in the urine and skin. O'Leary, Snell, and Bannick recently reviewed the literature and reported two cases with evidence of hepatic cirrhosis and portal obstruction which responded well when the arsenic was discontinued and symptomatic treatment was given. These cases, however, in contrast to Case II, showed practically no retention of dye in bromsulphalein tests of hepatic function, and a much better prognosis appeared indicated. The course in our case as manifested by the continued development of ascites and the repeated hemorrhages would indicate more extensive injury to the liver and the probability that the condition would progress in spite of any therapeutic procedures. At the patient's last visit the advisability of a Talma-Morison operation was considered, but she declined to have it done at that time.

Case III.—A man aged fifty-two years was first seen at the clinic May 11, 1925. He complained chiefly of jaundice of ten months' duration, together with progressive loss of weight and strength, and attacks, over a period of two years, of discomfort over the right subscapular area associated with bloating after meals. He had not had attacks of colic and had not vomited.

In August, 1924, the discomfort over the right side of the back became more severe, and following an elevation of temperature and a chill, jaundice developed. Recurrent attacks of chills and fever continued for two or three months. Meanwhile the jaundice gradually became deeper, and was associated with loose, light-colored stools, dark urine, and pruritus. For three months prior to admission he had been entirely free of pain.

On examination the patient weighed 154 pounds (normal weight 200 pounds) and the skin and sclerotics were icteric, graded 2. The edge of the liver could be felt 6 to 7 cm. below the right costal margin; it was hard but not nodular. The spleen was not felt.

The specific gravity of the urine was 1.025; it contained a trace of albumin, much bile, and an occasional pus cell. The hemoglobin was 55 per cent; the erythrocytes numbered 3,810,000, and the leukocytes 8,300. The Wassermann reaction of the blood was negative. A test of hepatic function showed retention of dye, graded 4. The serum bilirubin varied from 9.4 to 12.8 mg. for each 100 c.c.

A preoperative diagnosis of stone in the common bile duct with obstructive jaundice was made and exploration was carried out, May 22, 1925. The gallbladder was found to be contracted and inflamed, and to contain multiple stones. The common bile duct was tremendously dilated and contained a number of good-sized stones; stones were also present in the hepatic ducts and in the ampulla. The liver was somewhat cirrhotic. Cholecystectomy and choledocholithotomy with drainage were done. Following the operation the serum bilirubin gradually declined to 1.07 mg. for each 100 c.c. External biliary drainage persisted until July 7, 1925. While the patient was in the hospital the blood urea rose to 109 mg. for each 100 c.c., and the carbon dioxide combining power of the plasma declined to 22 volumes per cent. Vomiting, prostration, hiccoughs, and mental cloudiness followed. Glucose and sodium chloride solution intravenously, and alkalies were given, with slow improvement of the condition.

The patient returned, October 22, 1925. He had felt fairly well except that the jaundice had never entirely cleared. Six weeks before admission he had had an attack of general malaise and dull pain in the upper part of the abdomen, together with chills and fever of 101° F. This attack lasted about two days, and he had three or four similar attacks subsequently. Following these attacks jaundice increased and the stools became light colored.

On examination the skin and sclerotics were moderately icteric. The edge of the liver was palpable 3 cm. below the right costal margin. Urinalysis was negative except for the presence of bile. The hemoglobin was 66 per cent; erythrocytes numbered 3,820,000, and leukocytes 8,700. The serum bilirubin was 2.1 mg. for each 100 c.c., and the van den Bergh reaction was direct. The presence of another stone in the common bile duct was suspected, and on exploration, November 4, it was found that the common bile duct was thick-walled and contained considerable inspissated, thick bile, and that biliary cirrhosis was present. A T-tube was placed in the duct for drainage. Convalescence was stormy.

The patient returned again, June 8, 1926. There had been no drainage of bile for the preceding ten weeks, but the stools were of normal color. He

was in good general condition, but remained slightly jaundiced. The T-tube was removed.

The patient next returned July 2, 1928. He had remained in good health and had worked regularly since the last examination. Occasionally he would complain of weakness and his eyes would become yellow. December 17, 1927, March 6, 1928, and April 14, 1928, he had passed black tarry stools for a day or two, and then had had attacks of nausea and vomiting of dark blood. There was no pain, and chills or fever, with these attacks. He had not noticed any jaundice since December 17, 1927. Between these attacks he felt well.

The patient now weighed 174 pounds. The liver was slightly enlarged. The spleen was not palpable. Urinalysis was negative except for a slight trace of albumin. The hemoglobin was 70 per cent; the erythrocytes numbered 4,000,000 and the leukocytes 6,600. The serum bilirubin was 1.1 mg. for each 100 c.c., and the van den Bergh reaction was direct. A test of hepatic function showed retention of dye graded 1. The blood urea was 35 mg. for each 100 c.c.

The last examination at the clinic was made April 9, 1929. In December, 1928, the patient had had an acute respiratory infection and two weeks later edema of the right upper extremity had developed, with pain and fever. The swelling lasted about three weeks. Five weeks before admission he had had another "cold" and about one week later edema of the left side of the face developed which had decreased somewhat. April 11, 1929, edema of the left upper extremity developed, without pain, tenderness, or fever. Since February, 1929, he had noticed some distention of the abdomen.

On examination the patient appeared to be in good nutritional condition. There was slight swelling of the left side of the face and neck, more marked edema and cyanosis of the left hand, forearm, and distal half of the arm, and definite ascites. There was definite thrombosis of the left brachial and axillary veins which could be easily felt. Treatment was instituted for the relief of the edema and ascites. Ammonium nitrate was given in doses of 6 gm. daily, and intravenous injections of salyrgan were given at intervals of three days. An excellent diuretic response followed each injection of salyrgan, and the patient's weight fell from 168 pounds on admission, April 9, to 152 pounds, April 25. April 26, he suddenly became delirious, and rapidly progressed into a stupor, with the development of marked edema of the face, eyelids, and extremities. There was a definite decrease in the output of urine, but since the patient was incontinent, it was not possible to measure the output accurately. At intervals he would apparently become less stuporous but he would then toss about in bed in a restless and incoördinated fashion. Neurologic examination was unsatisfactory but did not reveal gross changes. Early on the morning of April 30, the patient suddenly regained consciousness, and the chemical constituents of the blood later rapidly returned to normal. He was dismissed from observation, May 3 (Table 1 on page 1446).

As has been mentioned, prolonged obstruction of the common bile duct may lead to cirrhosis. This is presumably due to

TABLE 1

SUMMARY OF DATA IN CASE III

Date.	Blood urea, mg. for each 100 c.c.	Carbon dioxide combining power of plasma, volumes per cent.	Blood chlorides, mg. for each 100 c.c.	Dye retention, grade.	Serum bilirubin, mg. for each 100 c.c.	Comment.
5/21/25	33			4	10.4	Before operation.
5/28/25					6.6	
6/ 2/25					4.9	
6/15/25					2.1	
6/23/25		22				Acidosis, and hepatic and renal disorders during convalescence.
6/24/25	72	24				
6/26/25	109	56			1.07	
7/ 3/25	71			3	0.92	
10/23/25					2.1	Before second operation November 4th.
11/12/25	119	45	495			Postoperative difficulty; intravenous treatment.
11/17/25	174	40	535			
11/20/25	83	54	568			
11/28/25	36	66	695			
7/ 2/28	35			1	1.1	Examination.
4/ 9/29	28			2	1.6	Ascites.
4/26/29	76	56				Onset of confusion and stupor.
4/29/29	140	44				
5/ 2/29	26					Recovery.

periductal inflammation from long-standing infection. McIndoe, by injection and corrosion methods, demonstrated the intertwining of the biliary and portal systems, suggesting the ease by which periductal fibrosis could interfere with the venous flow. However, factors other than mechanical processes must also be

considered in the explanation of ascites in hepatic disease, as suggested by the diuretic response to merbaphen in various types of edema and the effects of various diets as demonstrated by Bollman in experimental obstructive jaundice. It should be noted that the patient enjoyed two years of good health after relief of the obstruction of the common bile duct before the first signs of interference with the portal circulation developed.

Another point of interest in this case was the unusual postoperative complications. After the first operation the drainage tube was removed on the twenty-seventh day. On the fortieth day hiccough, vomiting, and weakness developed. The patient became prostrated and clouded mentally. The treatment was indicated by the condition of the blood, namely, the presence of acidosis and retention of urea. Prompt response followed the use of alkalies, glucose, and fluids. Convalescence was hastened with the closure of the biliary fistula. Walters and Parham described two clinical syndromes that may develop during convalescence from operations on the bile passages. In one there is increasing blood urea and bilirubin and decreasing excretion of urine and bile. In the other there is a profuse flow of light-colored bile, free excretion of urine, and dehydration. Some disorder of hepatic function is undoubtedly a part of these syndromes. This case is the only one we have encountered in which acidosis was recognized clinically and we have no explanation to offer as to the mechanism of its development. The complication after the second operation was somewhat similar but lacked the factor of acidosis. In both instances the liver must have played an important part. Recent work[5] shows that acetone bodies may accumulate in the blood in certain forms of jaundice.

Case IV.—A woman aged fifty years came to the clinic, May 17, 1929, because of abdominal colic and jaundice. One brother had been having indefinite attacks of abdominal pain associated with a yellow skin; between attacks she apparently had a sallow complexion. The patient had considered herself in good health up to the age of fifteen years; since then she had had recurrent attacks of colic in the right upper quadrant of the abdomen, accompanied by vomiting, and often requiring morphine for relief. At about the age of eighteen years she became jaundiced, and this had continued unin-

terrupted, becoming worse after attacks of pain, and then clearing somewhat. The stools had never been discolored and there had not been itching at any time. At the age of thirty-two years cholecystostomy had been done; much sandy material was present in the gallbladder. After the operation bile drained for about two weeks, but the jaundice cleared only a little. Except for a minor attack of pain shortly after she returned home and a "heavy feeling" in the stomach, with bloating and belching after meals, she remained fairly well for the next two or three years. She then began to have attacks of colic in the right upper quadrant with fairly long intervals between attacks. The jaundice increased following each attack of pain. Six years previous to admission, she had had a severe attack of pain, requiring morphine, after which she remained fairly well until January and April, 1929, when she again had severe attacks of pain with increased jaundice. The stools had never been acholic. Chills or fever had not accompanied the attacks. Her appetite was good and there was little loss of weight.

The patient weighed 128 pounds, and appeared to be well nourished. There was moderately deep jaundice of the skin and sclerotics. There was a scar over the upper part of the right rectus muscle, but neither the liver nor the spleen was palpable, and abdominal masses could not be felt. The hemoglobin was 70 per cent; the erythrocytes numbered 4,090,000, and the leukocytes 5,400. The Wassermann reaction of the blood was negative. The serum bilirubin was 5.2 mg. for each 100 c.c., and the van den Bergh reaction was direct. A fragility test of the erythrocytes was negative. Examination of the blood smear showed definite microcytosis. Roentgenograms of the area of the gallbladder were negative. A clinical diagnosis was made of chronic cholecystitis, obstructive jaundice, and stone in the common bile duct.

Exploration was done, May 22, 1929. The liver appeared to be in good condition, and the gallbladder was buried in adhesions from the former operation. The common bile duct was about three times normal size. The spleen was about four times normal size. The gallbladder was opened, but stones were not found. The common bile duct was explored, and a large scoop could be passed into the duodenum. A T-tube was put in the common bile duct, and a dressed tube into the gallbladder.

After the operation the serum bilirubin rapidly rose from 5.2 to 39.5 mg. for each 100 c.c., and then slowly declined to 12.8 mg. prior to the patient's dismissal, June 24, thirty-four days after operation. The drainage of bile from the tube continued for three weeks, although at times in small amounts, and then practically ceased.

The patient returned to the clinic, October 7, stating that the jaundice had gradually decreased, the stools had become normal in color and there had been little flow of bile. She had had two attacks of moderate upper abdominal distress associated with profuse flow of bile externally, lighter colored stools, and jaundice but no fever or chills. She still appeared well nourished and comfortable.

On examination there was moderate jaundice. The liver was not palpable, but the spleen could readily be felt 3 cm. below the left costal margin. The T-tube was removed, October 8, following which there was continuous drainage of a small amount of bile from the fistula. The stools remained

light colored, appetite decreased, and there was some nausea after eating but no vomiting. There was mild prostration. The urine contained tyrosine, as was shown by chemical test. However, the most striking feature was the rapid and extreme increase in jaundice. The serum bilirubin values are shown in Table 2. The patient was dismissed, November 4, 1929.

TABLE 2

VALUES FOR SERUM BILIRUBIN IN CASE IV

Date, 1929.	Serum bilirubin, mg. for each 100 c.c.	Blood urea, mg. for each 100 c.c.	Blood sugar, mg. for each 100 c.c.
10/ 8	12.5		
10/14	39.6		
10/15	52.0		
10/16	55.0		
10/21	60.0		
10/24	57.0		
10/28	45.6	23	
10/29	43.2	46	127
11/ 4	54.0		

This case is presented to illustrate difficulties of accurate diagnosis, the necessity of thinking anatomically, the unusual postoperative reactions, and the indeterminate etiology. It is also confirmative of a statement we have often made that the more cases of jaundice one observes the less confident one becomes in making a positive diagnosis. The history of repeated colic followed by jaundice and its associated features in a patient in good general condition is usually the result of calculi in the biliary tract. However, there are a few cases in which calculi cannot be demonstrated and the disease appears to be intrahepatic. Obstruction of the common bile duct was not demonstrated at operation, yet the subsequent symptoms of distress, increasing jaundice, light-colored stools, profuse discharge of bile externally, and the persistence of the fistula after removal of the tube suggested some intermittent mechanical difficulty

in the common bile duct below the site of the fistula. However, in addition to the absence of any demonstrable obstruction at operation, the extraordinary increase in jaundice after operation, particularly after removal of the T-tube, suggested that the principal pathologic process was intrahepatic. We cannot recall any case of true obstructive jaundice behaving similarly although in cases in which the obstruction has not been removed a slight increase in jaundice may occur at times.

The question of hemolytic jaundice was also raised, but the normal fragility of the erythrocytes and the direct van den Bergh reaction practically excluded it. The depth of the icterus, anorexia, nausea, and mild prostration during the patient's second visit suggested some process of the nature of subacute yellow atrophy. The presence of tyrosine in the urine tended to increase this suspicion. However, the unusual feature from this standpoint was the extreme duration of the icterus. The accumulation of clinical and pathologic data in such cases would greatly aid in the elucidation of many of the problems of this difficult group in which the jaundice appears to be of intrahepatic origin.

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CHRONIC ULCERATIVE COLITIS ASSOCIATED WITH SPLENOMEGALY

J. Arnold Bargen and Herbert Z. Giffin

It has long been recognized that enlargement of the spleen frequently occurs in association with acute infectious disease. It has not been generally emphasized in medical literature with the exception of the voluminous publications on amyloid disease in the days of chronic suppuration, that chronic, persistent or intermittent infections may produce chronic splenomegaly. Recognition of this fact led to the separation, by Giffin[4] in 1913, of certain cases simulating splenic anemia into a group classified as "chronic infectious splenomegaly." This grouping was observed in subsequent articles.[5, 6] It was shown, in cases of this type, that lasting benefit from splenectomy was rarely received. In the cases thus classified there was a history of chronic recurring endocarditis, chronic arthritis, furunculosis, peripheral thrombosis and abdominal thrombosis. In 1927[7] chronic colitis was added to the list of etiologic conditions. Syphilitic splenomegaly was likewise recognized as a chronic infectious condition which might simulate splenic anemia. Splenic enlargement in association with incipient syphilis and with hereditary syphilis have been commented on by Lesne and by Peiser.

Talley and Lindsey, in a study of splenic enlargement in chronic cardiac disease, suggested that distinct splenomegaly meant recurrent endocarditis, and Arnett in a study of 286 necropsies in cases of recurrent cardiac disease found the spleen often greatly enlarged. He noted that splenic enlargement was frequently found in noncardiac streptococcic infections. Hutcheson noted it in a case of multiple abscesses of the liver and thought it was probably the result of acute cholangitis. Felty

reported five cases of chronic long-standing arthritis in adults with splenomegaly and leukopenia, and made note of the striking and unusual picture which they presented. Opitz, Frick, and others reported splenomegaly with intra-abdominal thrombophlebitis.

The occurrence of diarrhea in some of the reported cases of splenic anemia, and the demonstration of actual colitis in later cases studied have led to the suspicion that this association between colitis and splenomegaly is more common than was at first believed. The case reported here exemplifies the development of splenomegaly during the course of true chronic ulcerative colitis.

REPORT OF CASE

A girl aged eighteen years came to the clinic in July, 1915, with bowel trouble which she said she had had since the age of seven, following a severe attack of measles. At that time bowel movements were averaging seven or eight every twenty-four hours; they were watery and mixed with blood and pus. Except for the first year, there had not been remissions, but the condition remained constant.

The patient's weight was 97 pounds, a weight which she had maintained for several years. She was thin, pale, and rather apathetic, with drawn features. She appeared older than her age. Her appetite was fair. She had had occasional night sweats but no cough or expectoration. There was some tenderness and soreness over the entire abdomen. A tumor corresponding to increased splenic dulness was noted, and the edge of what was thought to be the spleen was definitely palpable with ordinary respiration; it seemed firm. The hemoglobin at this time was 49 per cent. Erythrocytes numbered 4,100,000 and leukocytes 4,000, of which 58 per cent were polymorphonuclear neutrophils and 36.5 per cent small lymphocytes. The systolic blood pressure was 122, and the diastolic 60.

The patient's next visit to the clinic was in June, 1924, at which time her weight was the same and she said she did not feel as strong as she had for several years. The condition of the bowels was about the same. The hemoglobin was now 38 per cent; the erythrocytes numbered 3,410,000 and the leukocytes 5,100, of which 65 per cent were polymorphonuclear neutrophils. She was still rather debilitated and thin. The proctoscope showed a stricture involving the lower 5 cm. of the rectum, just admitting the index finger, and above the stricture the mucosa was granular and bled easily. There was a polyp 16 cm. above the anus. Roentgenograms of the colon by barium enema showed the deformity of chronic ulcerative colitis of the entire colon with marked narrowing. A roentgenogram of the thorax was negative.

The patient returned again in February, 1925, at which time her condition was found to be about the same except that the condition of her blood

had improved somewhat. The hemoglobin was 50 per cent; erythrocytes numbered 3,270,000 and leukocytes 4,400, of which 69 per cent were polymorphonuclear neutrophils. A culture from the rectal lesion made now for the first time yielded the usual diplostreptococcus found in cases of chronic ulcerative colitis. Vaccine was administered by the home physician.

The next examination was in March, 1927. This time the patient's weight was 99 pounds. The systolic blood pressure was 130, and the diastolic 60. The temperature was 99.8° F. on several occasions, and she spoke of definite improvement in the condition of her bowels; the rectal discharges now averaged about six in twenty-four hours and were without blood. She had not passed visible blood for a year. The tonsils had not been removed; they seemed to be infected, and one infected tooth was present which had been noted at the previous examinations. She made note of the fact that colds invariably caused exacerbation of the bowel trouble. Vaccine was continued and the infected tooth was removed. At this time it was noted that there was a movable, smooth, firm tumor in the left part of the abdomen, extending up under the left costal margin. The lower edge of the tumor, thought to be the spleen, descended almost to the iliac crest on deep respiration. It had increased greatly in size since 1915, the time of her first visit to the clinic.

The next visit in April, 1928, showed definite general improvement. The hemoglobin was 45 per cent; erythrocytes numbered 3,850,000 and leukocytes 5,900, of which 74.5 per cent were polymorphonuclear neutrophils.

With the extensive disease of the colon, its long duration, the destruction of the wall of the bowel, and the complications of stricture and polyposis, cure cannot be hoped for. The disease seems to be arrested. The chief clinical features are the long history of disease, its extent and gross injury to the bowel, the patient's debilitated appearance and yet fair general condition, and the progressive splenic enlargement which seems to have increased apace with the duration of the disease. This would suggest the possible need of the splenic elements in combating the infection on the assumption that as destruction of the spleen continued an increase in size resulted from degeneration, regeneration, and fibrosis.

The question of why splenomegaly develops in certain cases of colitis and not in others cannot be answered, but it leads to the supposition that certain bacteria, whether the primary organisms or secondary invaders, or possibly certain toxins, have an "affinity" for splenic localization.

A case of this type coming under observation during a latent

period, so far as the colitis is concerned, might logically be regarded as a case of splenic anemia. Experience, however, suggests that when a history of chronic infection is present, splenectomy may be followed by an exacerbation of the infection and at best eliminates only a small portion of the infected tissue, and probably a portion of only secondary importance. Most of the patients with chronic infectious splenomegaly which we have observed have later died of nephritis. Patients with colitis are most likely to die of recurrence.

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PREGNANCY FOLLOWING SPLENECTOMY

ROBERT D. MUSSEY AND GEORGE G. BURKLEY

SPLENECTOMY has not been practiced long enough to receive much consideration with regard to pregnancy that may follow the operation. One patient was under our supervision during the illness which necessitated splenectomy, following splenectomy, and subsequently through pregnancy and confinement. This case is reported herewith.

The patient, a woman aged twenty-nine years, presented herself at the clinic September 9, 1926, complaining that she "bruised easily." This condition had been noted for a period of thirteen years. The bruising never occurred spontaneously, and pain, other than that due to the trauma itself, had not been present. Her general health had been good. On one occasion, following the extraction of several teeth, there had been slight oozing of blood for five or six days. The menstrual periods had never been excessive, but on several occasions clots were passed.

General examination was negative, except for several large areas of ecchymosis in various situations on the body, and small petechiæ over the neck and thorax. Roentgenograms of the teeth revealed several with apical infection. Examination of the blood showed that the hemoglobin was 70 per cent; erythrocytes numbered 4,610,000 and leukocytes 13,500. The percentages in the differential count were as follows: lymphocytes 29.5, large mononuclears 0.5, neutrophils 68, eosinophils 1.5, and basophils 0.5. The coagulation time (Boggs) was found to be seven minutes, and the bleeding time eleven minutes; the platelets numbered 256,000. There was no evidence of retractility of the clot at the end of one hour, and retraction was incomplete at the end of two hours (test incomplete). The prothrombin time was as follows: coagulation of 2 drops after thirteen minutes, of 3 drops after thirteen minutes, of 4 drops after seventeen minutes, of 5 drops after seventeen minutes, of 6 drops after twenty-one minutes, of 7 drops after twenty-two minutes, and of 8 drops after twenty-five minutes. The platelet count a week later on three successive days ranged from 124,000 to 72,000, the coagulation time from four and a half to eight minutes, and bleeding time from three to nine and a half minutes. These were taken twice daily. Blood grouping was Type IV. The infected teeth were extracted October 19 without ill effects. Coagulen had been given to the patient for several days previous to the extraction.

April 1, 1927, on account of profuse menorrhagia, the patient was admitted to the hospital. Aside from several purpuric spots, the general examination did not reveal anything abnormal. The bleeding was controlled by ergot and, April 12, a transfusion of 500 c.c. of blood was given by the sodium citrate method. The results of examination of the blood while the patient was in the hospital are given in Table 1.

TABLE 1

EXAMINATION OF BLOOD IN HOSPITAL

Date, 1927.	Hemoglobin, per cent.	Erythrocytes, millions.	Color index.	Leukocytes, thousands.	Platelets, thousands.	Coagulation time (Boggs), minutes.	Bleeding time, minutes.
4/ 3	45	2.53	0.8	11.2	108	6	3.5
4/12.	40	3.17	0.6+		56		
4/14*	42	3.24	0.6+	5.9	50		

*Retraction of the blood clot was incomplete after five hours.

Menorrhagia recurred and, June 1, 1927, a second transfusion of 500 c.c. of citrated blood was given and curettement was done. Microscopic examination of the material obtained showed chronic hypertrophy of the endometrium. The menorrhagia continued, and rectal bleeding occurred. Proctoscopic examination showed submucous hemorrhagic extravasation scattered diffusely through the walls of the rectum and sigmoid. There were normal pink areas 5 mm. in diameter. The condition was much like melanosis, except that the pigment was red. There was no break in the mucosa other than the anterior wall, where there was a small break, probably caused by traumatization with the tip of the syringe used in giving enemas. The proctologist reported that he had never seen a similar condition. A diagnosis was made of rectal and sigmoidal purpura.

Splenectomy was advised on account of the persistence of menorrhagia, the appearance of rectal bleeding, persistence of petechiæ, increasingly marked anemia, continued low platelet count (9 to 18 counts less than 100,000), and the fact that retractibility of the blood clot was persistently incomplete in five hours. The patient was operated on December 3, 1927. The surgeon reported that the spleen was about three times normal size, dark and of the "blood-destroying" type. It was removed without much difficulty. The appendix, which was chronically inflamed, graded 2, and greatly thickened, was removed. The pathologist reported mild chronic splenitis with dilatation of sinusoids and congestion of the pulp, and catarrhal appendicitis with obliteration of the mucosa of the distal portion. Recovery was uneventful, and the patient was dismissed from observation, December 17. Following this there was progressive improvement of the condition.

January 2, 1929, the patient presented herself for examination, and pregnancy of about three and a half months was discovered. Her general

condition at that time was good. On account of mild secondary anemia and in consideration of her previous history she was given liver extract during pregnancy.

The patient was under observation through an uneventful pregnancy, and was admitted to hospital in labor, July 9, two weeks later than the calculated date. The first stage of labor was protracted; it lasted more than twenty-four hours. Then, on account of the patient's increasing exhaustion, and the persistence of right occipitoposterior position of the fetus, the membranes were ruptured artificially, manual rotation to the right occipitoanterior position was effected, and delivery was completed by forceps. A right median-lateral episiotomy was done and repaired with chromic catgut. Following delivery both the mother and babe were in good condition.

The puerperium was normal in every respect. Results of examination of the blood are shown in Table 2. The patient reported, October 21, 1929, that she was in excellent health, and that the baby was doing well. Purpuric symptoms had not been noted.

TABLE 2

CONDITION OF THE BLOOD DURING PREGNANCY AND PUERPERIUM

Date, 1929.	Hemoglobin, per cent.	Erythrocytes, millions.	Color index.	Leukocytes, thousands	Coagulation time (Boggs), minutes.	Bleeding time, minutes.	Platelets, thousands.
Prepartum. 1/10	69	4.22	0.8+	17.3			176
3/ 4	68	3.85	0.8+	16.4	3	12	
4/ 3	51	4.06	0.6+	12.6			
4/12	65	3.90	0.8+	17.6			
5/ 6	64	3.81	0.8+				
5/20	60	3.71	0.8+		3.5	1.5	
6/ 3	58	3.88	0.7+	18.6			
Postpartum. 7/11	75	5.48		14.8			
8/ 9	56	3.63	0.7	8.2	6	1.5	180
8/15	70	4.26		8.2	6	1.5	180

COMMENT

Of 214 operations of splenectomy performed on women at The Mayo Clinic, ninety-eight were performed on women who

were, or are now, within the child-bearing age, which was set arbitrarily between sixteen and forty-five years. A questionnaire was sent to this group of patients inquiring concerning the pregnancy of those married at the time of splenectomy, or married since splenectomy. In eighty replies received, fifty-seven patients reported that pregnancy had not occurred; however, some had used precautions because of splenectomy, and fifteen were not married.

Twenty-three women reported thirty-two pregnancies. Twenty-eight living babies were born to twenty of these women; one woman had had four babies, one had had three, and two had had two babies each. All of these women had had normal pregnancy, labor, and puerperium except two, one of whom had a living baby following cesarean section for a contracted pelvis, and one who, although threatened with abortion at the second month, progressed safely to the termination of pregnancy. Of the remaining three patients, one patient had had an abortion with severe hemorrhage at the third month, one had had a severe gastric hemorrhage during pregnancy and two months later premature labor with a dead baby at the seventh month, but without abnormal bleeding, and one had had marked edema and albuminuria during pregnancy with prompt relief following termination of pregnancy, at the seventh month. This patient has recently completed an uneventful pregnancy. In one case splenectomy was performed at the fourth month of gestation without disturbing the course of the pregnancy. The baby, born five months later, and a baby born subsequently are well.

The children of these women, with three exceptions, have been and are apparently normal. One baby lived only one day. One was never strong and died at the age of one year; a diagnosis of hemolytic jaundice was made by the family physician; a child born subsequently is normal and well. One had splenectomy for hemolytic jaundice at the age of seven years.

The conditions for which the spleen was removed were as follows: hemolytic jaundice, eight patients; splenic anemia, eight patients; purpura hemorrhagica, three patients; hemor-

rhagic cyst of spleen, Gaucher's disease, syphilitic splenomegaly, and "wandering spleen," one patient each.

In a search of the literature of the last ten years, only one article was found, that of Barsalou, who reviewed the literature up to 1922 and reported the case of one patient who had had two pregnancies following splenectomy. He found recorded in the literature eight cases of pregnancy following operation (splenectomy doubtful in two) and one case in which splenectomy was done during pregnancy. He also mentioned briefly some experimental work on the subject. He concluded that splenectomy is not a contraindication to normal pregnancy and delivery; that changes in the blood are within normal limits (decreased erythrocytes, increased leukocytes, and decreased percentage of hemoglobin), and that the children do not show abnormalities, either at birth or later, which could be attributed to the maternal splenectomy.

SUMMARY AND CONCLUSIONS

Following splenectomy, twenty-three women had thirty-two pregnancies. Twenty-eight living children were born, and two miscarriages and two premature labors occurred.* The course of pregnancy, confinement, and puerperium in this group of women does not show appreciably more evidence of departure from the normal than that of an average group of pregnancies. The occurrence of pregnancy was followed by recurrence of symptoms in only one case, one of Banti's disease, in which gastric hemorrhages had occurred prior to removal of the spleen, and once during pregnancy.

There seems to be slightly more than the normal hazard

* A report received after this article had gone to print informed us of a second patient who had had cesarean section for a cause not known to us, and another who had had splenectomy for splenic anemia at the third month of pregnancy. This patient died of a "stroke of paralysis" fifteen days after the delivery of a normal child at term. In this group of cases those of splenic anemia were evidently subject to more complications than the average cases of pregnancy, as the pregnancy was followed by the recurrence of symptoms in three cases of splenic anemia, in two of which hemorrhages had occurred during pregnancy. In one of these and in a third case hemorrhages occurred subsequent to pregnancy.

for the fetus, and this seems to be due to the disease for which the splenectomy was done rather than to the removal of the spleen. Of thirty-two pregnancies there were four fetal deaths, two babies died within the first year, and one child required splenectomy for hemolytic jaundice at the age of seven years. On account of the familial tendency to the occurrence of hemolytic jaundice, test should be made of the fragility of the erythrocytes in the case of any child who has been born to a parent with hemolytic jaundice.

The question may be raised of the safety of pregnancy in a group of patients whose spleens were removed on account of severe gastric hemorrhages. Of eight cases of splenic anemia, including one case in which the condition had advanced to the stage of Banti's disease, there were severe gastric hemorrhages prior to pregnancy in four cases; in two of which hemorrhage occurred during pregnancy. Injury to the liver, which may be present in this group and in Gaucher's disease, may add to the hazard of pregnancy.

It is probable that any hazard to pregnancy is due to the disease for which the spleen is removed rather than to absence of the spleen. In purpura hemorrhagica it seems evident that removal of the spleen greatly decreases the hazard of pregnancy.

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CHRONIC ULCERATIVE COLITIS: ITS ROENTGENOLOGIC MANIFESTATIONS

HARRY M. WEBER

AT The Mayo Clinic it has been the practice in the investigation of a colon suspected of being the site of chronic ulcerative colitis to use the barium enema, employing a fairly thin emulsion of barium at a temperature corresponding as closely as possible to that of the body. The barium meal shows nothing more than rapid emptying, and it is impossible, with it alone, to obtain a satisfactory idea of the contours of the lumen, and the condition and size of the bowel. The proper preparation of the patient is an important factor, because in spite of numerous evacuations, small clumps of foreign material adhering to the wall of the bowel are confusing, and if numerous and generously distributed may closely simulate the mottled appearance of generalized polyposis. Large accumulations of fecal material, fluid and gas obscure the field to such an extent as to preclude satisfactory interpretation. The added burden of a dose of castor oil and enemas to a patient already afflicted with profuse and frequent rectal evacuations will seem superfluous, but even in these patients the presence of foreign material in the bowel has so often been confusing that a special effort at complete evacuation and cleansing of the bowel is expedient. The necessity for this is further emphasized by the fact that in those cases in which the disease is confined to the lowest segments of the bowel, constipation may be present, and an unprepared patient may have an obstructing mass of feces above the involved portion.

As the barium enema enters the bowel, the filling of the rectum must receive closest attention, because in about 20 per cent of cases the disease is confined to this area alone. If the

disease is acute and not of long standing there may be no roentgenologic evidence whatever, or the only sign may be that of extreme hyperirritability. The patient will not be able to retain the enema long, so violently does the inflamed mucous membrane resent anything in contact with it. Usually, however, by sustained effort he will be able to retain the enema sufficiently long to permit filling of all of the colon, but by the time a roentgenogram has been made the rectum will have been emptied, leaving only the colon above the rectosigmoid juncture filled. This gives a characteristic picture: the ampulla, with enough barium adherent to its walls to show its contour, is markedly narrowed and exhibits a series of coarse linear striations which are the shadows of barium retained in the folds of the vigorously contracted bulbous ampulla. As the disease progresses, either with long continuation of the infection or after repeated exacerbation and secondary infection, the characteristic thickening, contraction and shortening takes place, and the bulbous shadow of the normal broad ampulla may be changed to one which is narrow, straight, and tube-like. When severe polyposis is present the characteristic mottling or stippling of the contours makes its appearance: although this shadow is pathognomonic, it is a difficult sign to elicit in the rectum, both on account of the size of its lumen and its inaccessibility to palpation. It can be simulated by two conditions: by flecks or small clumps of feces or inspissated mucus adhering to the lumen, or by patches of comparatively undestroyed mucous membrane which sometimes protrude from the lumen of the bowel in tall islands when the ulceration has been very marked and deep, and coalescence of the individual ulcers has taken place. Even the proctologist sometimes has difficulty in distinguishing these abnormalities from polyps. Roentgenologically both are distinguishable from polyps by their irregularity in size and shape and their comparatively uneven distribution, and from each other by the fact that the mucosal islands are scarcely ever numerous, are unevenly distributed, and are found constantly on repeated examinations.

Bargen[1] has found that the entire colon is affected in 46.5

per cent of the cases, that the portion from the rectum to the descending colon is involved in 11 per cent, from the rectum to the splenic flexure in 12 per cent, and from the rectum to the hepatic flexure in 11 per cent. The pathognomonic picture presented by an advanced case or one in which there have been repeated acute exacerbations and secondary infections has often been described. Schwarz, in 1914, gave an accurate and vivid description of a few cases which had come under his observation at that time, and shortly before him Stierlin described the roentgenologic appearance of a similar case. In a typical, well-

FIG. 230.—Chronic ulcerative colitis involving the entire colon. Right colon filled with secretion and fecal residue.

advanced case one is struck with the rapidity with which the colon fills; the ileocecal valve is reached in an instant, and if the cecum is involved, the valve is always patent. The colon itself is small in caliber, and if ever there was any redundancy it has disappeared; both the size of the lumen and the length of the colon have been reduced (Fig. 230). As a rule the colon will be markedly ptosed, in the sense that its mooring points, which are normally high up, below the diaphragm, at the splenic flexure

and at the position of the phrenicocolic ligament, are obviously displaced downward. Its course is exceedingly straight, and the angles at the flexures approximate right angles. From a soft, pliable, thin-walled, gently winding, and twisting tube, it has become a thick-walled, hard, inflexible, stiff, straight pipe with a small lumen somewhat analogous in form and general appearance to a thick-walled, tense, sclerotic artery. This picture is not easily confounded with that of any other disease of the colon (Fig. 231).

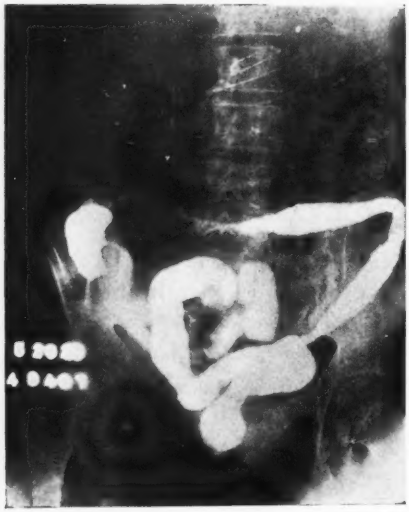

FIG. 231.—Severe involvement. Shortening of the colon, displacement of the hepatic and splenic flexures, and spastic narrowing of the proximal portion of the transverse colon may be noted.

In general, the appearance of the colon varies with the virulence and stage of the infection, the amount of injury, the extent of involvement, and the presence or absence of complications such as polyposis, strictures, malignant changes, and secondary infection. In the earliest stages spasm may be the only manifestation. This is due to the irritability of the ulcerated bowel, and, depending on the extent of the disease, may be local or diffuse.

In this stage, and if spasm is the only sign present, the roentgen ray will not distinguish chronic ulcerative colitis from other ulcerating diseases of the colon. It is rare, however, to see a case of chronic ulcerative colitis in which at least some of the other signs of the disease have not appeared. A fairly acute case will show at least some of the typical signs, such as rapid filling, marked narrowing of the lumen, and absence of haustration.

Occasionally one or several contracted areas are seen, giving the bowel the appearance often described as that of a string of sausages. The constrictions may be genuine organic strictures or may be due entirely to localized spasm. Spastic constrictions tend to vary in situation and appearance, at different times, and are likely to disappear entirely, or at least to diminish in intensity, after the administration, to physiologic effect, of a suitable antispasmodic.

Destruction of the mucous membrane gives a varied appearance, depending on its extent and the depth of the penetration. If the regions of ulceration are superficial the contour may be entirely smooth; if they are deeper, the outlines of the colon are feathery or furry and have a moth-eaten or fringed appearance. If the ulcerations are very deep the contour has an entirely different appearance; it is rough and uneven, and many niche-like projections are seen extending out from the wall of the bowel (Fig. 232).

Polyposis occurred in 13 per cent of Bargen's series.[3] This complication gives the characteristic appearance described previously, and is easily demonstrated in the more proximal portions of the colon, especially in the most accessible and easily palpated descending portion. The polyps vary extremely in size and number, but all give a similar appearance in the roentgenogram, namely, a rarefied area in the shadow of the colon (Fig. 233). Mottling or stippling, either localized or general, is the characteristic sign either of very numerous small polyps, or of general hyperplasia of the mucosa.

It is extremely important constantly to bear in mind the occurrence, rare as it is, of localized areas of chronic ulcerative

FIG. 232.—Chronic ulcerative colitis, fulminating type. The deep, perforating ulcers are seen as niche-like projections from the margins.

FIG. 233.—Chronic ulcerative colitis with extensive polyposis. The mottled appearance seen in the transverse and descending colon is characteristic.

colitis in isolated segments of the colon, without involvement of the distal segments and rectum (Fig. 234). This occurred in 3 per cent of Bargen's series of cases. The areas involved vary in size and when small may offer considerable diagnostic difficulty. Roentgenologically the picture is typical, the involved segment is narrow and usually smooth, although when the involvement is acute and very virulent the contours are moth-eaten and feathery in appearance. It will be found difficult to

FIG. 234.—Chronic ulcerative colitis without rectal involvement. The entire colon proximal to the sigmoid portion is involved.

maintain constant filling of the involved portion due to its marked hyperirritability, and a malignant or tuberculous filling defect is closely simulated (Fig. 235).

A rapid change in symptoms, to obstruction, cachexia or anemia, leads the clinician to suspect malignancy. If malignancy is present, it probably has developed on a basis of polyposis. In addition to the characteristics of chronic ulcerative colitis, a definite filling defect, obstruction, or marked irreg-

ularity appears somewhere along the course of the ulcerative process. Twenty cases in which there was malignant change have been observed at The Mayo Clinic; there was multiple carcinoma in six cases, and diffuse carcinomatosis along the entire course of the bowel in one case.[2] The age incidence in these cases is worthy of note. Five patients were aged fifty years or more, six were between the ages of forty and forty-five, six were between the ages of thirty and thirty-nine, and three

FIG. 235.—Chronic ulcerative colitis confined to a segment of the transverse colon. An ileotransverse colostomy had been attached proximal to the lesion which was mistaken for carcinoma.

were between the ages of twenty and thirty. The filling defect is similar to that seen otherwise in ordinary malignant disease of the colon, and the diagnosis of a malignant lesion is based on interference with the progress of the enema by the constricting lesion, canalization through the irregular filling defect, and the presence of a localized palpable mass.

Tuberculous colitis, amebic ulcerative colitis and chronic ulcerative colitis are the most common nonmalignant conditions

of the colon offering differential diagnostic difficulties, although typical cases of each present pictures so different from one another that errors in interpretation are not ordinarily made. The course of events in their pathologic development, especially as it pertains to the site and the order of progression of the disease, forms the cardinal point of differentiation. Chronic ulcerative colitis, as has been pointed out, usually begins in the rectum and progresses thence proximad until the entire bowel is involved. Tuberculous colitis and amebic ulcerative colitis, on the other hand, have their inception in the most proximal positions of the colon, the former primarily in the small intestine, and progress distad. Both produce marked hyperirritability of the involved portion of the bowel and usually show involvement of considerable extent. The filling defect of the hyperplastic type of intestinal tuberculosis which is the result of marked spastic manifestations superimposed on severe infiltration of the wall of the bowel presents a picture not likely to be confusing. Primary tuberculosis of the bowel in the absence of active pulmonary tuberculosis must be extremely rare, and I have not seen primary tuberculous involvement of the distal portion of the colon without marked involvement of the proximal portion, although tuberculous lesions of the distal portion of the colon secondary to active urogenital tuberculosis have come under my observation. Cases of amebic colitis with roentgenologic evidence of its presence have not been common in my experience, and the lack of signs is due most probably to the comparatively mild form of the disease prevalent in this latitude. When it is present, the roentgenologic appearance resembles closely that of chronic ulcerative colitis; the bowel is hyperirritable, haustra are markedly subdued, and the contours of the mucous membrane are fringed and furry; unlike chronic ulcerative colitis, however, the colon preserves its pliability, thickening of the wall is not present to the degree shown in chronic ulcerative colitis, and peristalsis is not so markedly interfered with. The whole process does not give the impression of such marked severity.

Syphilitic infection of the colon is infrequently encountered, but if present can simulate closely the picture of localized chronic

ulcerative colitis. There is even, diffuse, concentric narrowing of the lumen, involving a considerable extent of the bowel. Evidence of hyperirritability is not present, however; the remainder of the bowel is entirely normal, and involvement of the mucosa is not evident, since the lesion is entirely extraluminal and does not tend to ulcerate. There are certain other conditions of the colon in which the lack of haustra may be a confusing factor, and this is the case particularly if one depends

FIG. 236.—Absence of haustra and some narrowing of the colon distal to the splenic flexure. Chronic constipation; normal rectal mucosa.

solely on roentgenographic data. In patients who complain of chronic constipation occasionally roentgenologic examination will reveal a smooth, unhaustrated colon due probably to temporary relaxation of the long muscle bands. This is not constant, however, and can scarcely be relied on as significant of colonic dysfunction. The descending colon, in which haustra are normally less pronounced and less visible than in the remaining portions of the colon, may be especially confusing in this respect

(Fig. 236). Carcinoma, actinomycosis, and diverticulitis not infrequently will imitate chronic ulcerative colitis.

The contribution of the roentgenologic method to the diagnosis of chronic ulcerative colitis is not a minor one. Proctologic observations give the most important diagnostic data when the rectum is involved, but the roentgenologist determines the extent of the process beyond the range of the proctologist, and accurately determines the presence or absence of complications;

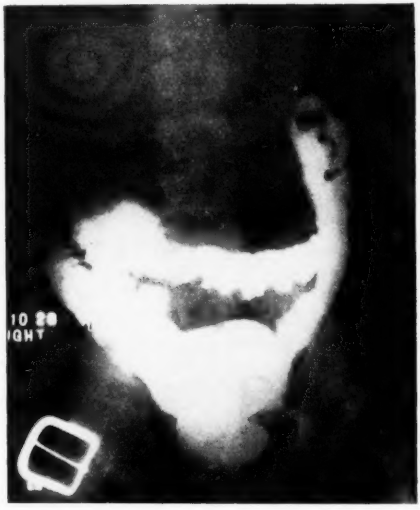

FIG. 237.—Chronic ulcerative colitis, fulminating type. Compare with Figure 232. Roentgenogram made January 10, 1928.

he follows the course of the disease and sees the efficacy or futility of therapeutic efforts (Figs. 237 and 238); and in those cases, comparatively rare as they may be, in which the rectum is not involved, the roentgenologic method offers the only reliable objective evidence of the presence of the disease. The method fails to give positive signs only in those cases in which the disease is confined to the rectum and most distal portion of the sigmoid.

FIG. 238.—Same case as that shown in Figure 237. Roentgenogram made three weeks later. Return of normal haustra in the descending colon, and marked improvement in appearance of the transverse colon after treatment may be noted.

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INFLAMMATORY LESIONS OF THE RECTUM AND COLON

PHILIP W. BROWN

I WISH to present four cases to illustrate not uncommon, and yet confusing, lesions of the rectum and colon. Much stress recently has been laid on the early recognition of carcinoma and on the diagnosis of ulcerative colitis. I do not desire to minimize these teachings but to emphasize that there are other conditions which closely simulate carcinoma and ulcerative colitis, and that accuracy in diagnosis of lesions of the bowel is essential to proper treatment. Carcinoma of the rectum is preferably treated by permanent colostomy and posterior resection of the rectum, yet this would have been a grave procedure if it had been carried out in Cases II, III, and IV presented here. Likewise, chronic ulcerative colitis is properly handled by administration of serum and autogenous vaccine; yet neither is of much value in amebic colitis, such as is illustrated in Case I.

REPORT OF CASES

Case I.—A man aged forty-eight years came to the clinic with the complaint of bloody diarrhea which had been present for two years. Prior to this he had had marked constipation. The onset of the diarrhea had been gradual, with six to eight stools daily. This had increased, and the bowels had moved frequently, both day and night. Weakness and anemia had increased until one day he had collapsed on the street while in Florida, where he had gone for his health. All manner of diets, blood transfusions, and the usual nonspecific measures had been tried. A diagnosis of chronic ulcerative colitis had been made and, although the diplococcus of Bargen had not been isolated, a vaccine had been made from cultures of a streptococcus that had been found. Otherwise, his history is of no moment except that he had been taking 60 drops of tincture of opium daily for twenty-one months.

Examination at the clinic revealed that the patient was thin, pale, and anxious, but otherwise nothing abnormal was found. Examination of the

urine gave negative results. Concentration of hemoglobin was estimated at 45 per cent (Dare); erythrocytes numbered 4,230,000, and leukocytes 12,700 for each cubic millimeter of blood.

Proctoscopic examination revealed a granular, easily bleeding mucosa and contraction of the lumen of the bowel to 50 per cent of its normal diameter. Discrete ulcers could not be seen. Cultures for Bargen's diplococcus were taken and later were reported negative. A roentgenogram of the thorax revealed an old, healed tuberculous process of the right apex. Roentgenologic examination of the colon disclosed abnormalities in the entire colon, such as occur in cases of chronic ulcerative colitis. In the study of the stool many *Endamœba histolytica* were identified.

The customary treatment by intermittent courses of emetin hydrochloride and treparsol was given. The opium was discontinued. Gradual resumption of a full diet was ordered. Following completion of treatment with 10 grains of emetin and 6 gm. of treparsol, repeated examinations of the stool were negative for *Endamœba histolytica* and the proctoscopic examination showed marked improvement with the lumen almost of normal diameter. The mucosa of the lower part of the rectum was glazed, but it did not bleed as easily as formerly and bleeding occurred chiefly along the edges of the valves. A second culture for the Bargen diplococcus was negative. The patient expressed himself as being "1000 per cent better." He was dismissed from observation and was advised to have administered to him 4 more grains of emetin and 9 gm. of treparsol in divided courses of 3 gm. to the course.

The proctoscopic and roentgenologic data would certainly lead one to make a diagnosis of chronic ulcerative colitis. In the past unsuccessful efforts to isolate Bargen's diplococcus had been made. Cultures at the clinic likewise were negative. Repeated examinations of stools had given negative results, and it may be merely fortuitous that the first specimen was almost alive with *Endamœba histolytica*. It is the custom at the clinic invariably to examine stools on two or more successive days in all cases of chronic ulcerative colitis, for in about 5 per cent of cases *Endamœba histolytica* is present. In such cases antiamebic treatment is indicated. The treatment must be watched carefully as true ulcerative colitis not infrequently is made worse by any treatment with an arsenical preparation.

This case also illustrates another exceedingly significant point concerned with the long-continued use of opium. This is always serious and it may not always be as easy to stop the patient taking opium as it was in this case. It is a measure that I strongly protest against and feel that almost any form of

treatment, no matter how apparently absurd, should be undertaken before the patient is given opiates for any considerable length of time. In practically any case of diarrhea there is relatively little danger in giving 4 grains of emetin hydrochloride, so that if laboratory facilities are lacking or inadequate, this drug may be used on an empiric basis. The response of amebic colitis to 3 or 4 grains of emetin continues to be one of the marvels of therapeutics, and the recollection of this may occasionally prevent an error.

Case II.—A woman aged forty-five years complained chiefly of a growth in the rectum. Her knowledge of this dated back only four weeks when she first had noted bright red blood with movements of the bowels. A moderate degree of rectal tenesmus had developed, with frequent passages of bloody mucus. Nine months before she came to the clinic she had first noticed a red vaginal discharge, although menopause had taken place more than two years before that. A diagnosis of carcinoma of the cervix had been made and had been proved by biopsy. Radium had been administered four times, at intervals of two weeks. She reported that for the last two treatments the radium had been handed to her and she had taken it home and inserted it in the vagina for the prescribed number of hours. Since the radium treatment, there had been no further bloody vaginal discharge. She had gained in weight and had been in apparent good health until the onset of the rectal bleeding.

The general examination revealed essentially normal conditions. On special examination, high in the pelvis, posteriorly, the palpating fingers transmitted a sense of infiltration, but otherwise vaginal examination, by palpation and inspection, revealed only normal conditions. On digital examination of the rectum there was felt, rather high and anteriorly, a moderately soft mass which did not have the usual "feel" of carcinoma of the rectum. Through the proctoscope, a large ulcerated area was seen which was considered to be factitious (radium ulcer).

In view of the good local result in the cervix and the presence of rectal ulcer, further irradiation was not advised for the time being. Local treatment for the rectal ulcer was carried out and after an interval of two weeks some improvement had been made. On dismissal the patient was advised concerning continuation of the rectal treatment.

Inflammatory lesions of the rectum, following the application of radium in the vagina, occur from time to time. Correct dosage and careful usage in the hands of experts have done much to minimize this complication. It is remarkable that this patient was permitted to insert the radium herself at her last two treatments, although this may not have been of any sig-

nificance in the development of the ulcer. Bleeding from the rectum following the vaginal use of radium should always arouse the suspicion of the possibility of a radium ulcer or of the more diffuse proctitis that occasionally is seen. Furthermore, the history of a malignant condition of the cervix, the discovery of infiltration in the left side of the pelvis, and a "peculiar feel" on rectal examination should all combine to make one slow to give a diagnosis of carcinoma of the rectum.

The prognosis in this case is guarded. If the malignant tissue has been completely destroyed, the rectal ulcer eventually will heal although it may take months. If there is recurrence, further radiotherapy will be attended with the risk of increasing the rectal trouble and thereby increasing the patient's suffering. I am not implying that treatment could not be administered, but the dosage and manner of treatment would need particular care.

Case III.—A woman aged sixty-five years presented herself with the complaint of rectal trouble of which she had been aware for about two weeks. Prior to this, she had undergone laparotomy on three occasions for conditions which had no bearing on the present complaint. Seven years prior to admission she had had a rectal abscess which apparently had cleared up in a short time. Her rectal trouble was indefinite itching and discomfort. Movements of the bowels were normal and no blood had been noted. After a week she had begun to worry over the possibility of carcinoma and had consulted her physician. A tentative diagnosis of rectal carcinoma had been made. Besides the rectal trouble she had suffered for ten years with substernal pain radiating down the left arm. This pain was produced by effort and was relieved promptly by resting. Dyspnea occurred on slight exertion.

The blood pressure was 160 systolic and 102 diastolic. The aortic second sound was accentuated and the heart was enlarged to the left. On digital examination of the rectum, firm nodules were felt on the left rectal wall just within the anus. Urinalysis, blood count, and Wassermann reaction of the blood all gave negative results. Roentgenologic examination of the thorax and colon did not reveal abnormality. The electrocardiogram did not show significant changes. On proctoscopic examination the nodular area was seen to lie beneath the mucosa, without evidence of ulceration. Several specimens were removed for microscopic examination and this was repeated a few days later. The pathologic report on all specimens was "chronic inflammatory tissue with lymphoid hyperplasia." Local treatment and daily hot irrigations were instituted, and after two weeks very little remained other than a nodular scar. The patient was dismissed with advice to continue hot irrigations and to be reëxamined in the near future.

With the history in mind, the question immediately arose as to what would be the best thing to do. The patient constituted a bad surgical risk from the cardiovascular standpoint and her not unnatural fear of radical operation did not simplify the problem. She impressed one as having about given up hope. The digital examination, aided further by visualizing the lesion with the proctoscope, revealed several nodular areas beneath the rectal mucosa. The nodules seemed to be discrete. These clinical observations, in addition to the suggestive point in the history of no blood having been passed, suggested that the lesion was benign, and this was confirmed by biopsy on several occasions. The relief that this diagnosis gave to the patient can well be imagined.

It is difficult satisfactorily to explain these inflammatory lesions. Buie has taught that following rectal or perirectal inflammation or after hemorrhoidal injections, these peculiar submucosal lesions may occur. In this case the cause may be the rectal abscess of seven years before. One must not overlook the possibility of a sarcoma of the rectum. There may be criticism of the advisability of doing a biopsy in the face of a possible malignant lesion, yet in certain cases, such as this, it is justifiable.

Case IV.—A woman aged sixty-three years came to the clinic primarily because she had been told that she had a carcinoma in the rectum. Her chief complaint was that for ten years she had had recurring attacks of epigastric pain, evidently brought on by constipation and relieved by defecation. She had always had more or less indigestion of an indefinite type. Six years before she came to the clinic, cholecystitis had been diagnosed, but at operation the gallbladder had been normal and appendectomy had been done. Four months prior to admission, she had had copious hemorrhage from the bowel, of bright red blood. There had been two more—less copious—hemorrhages in the next twenty-four hours. After a rest in bed for ten days, roentgenologic studies of the gastro-intestinal tract and proctoscopic examination had been made, but nothing had been found to explain the bleeding. An exploratory operation had been undertaken, but nothing significant had been found at that time. She had convalesced uneventfully and had remained well until three years before she came to the clinic when further bleeding from the bowel had begun. On reëxamination a diagnosis of carcinoma of the rectum had been made.

The general examination revealed that the patient was in essentially

normal condition for her age. On digital examination of the rectum an indefinite sensation, as of a mass, was transmitted by the fingers, but the mass was too high for satisfactory examination. Roentgenologic studies of the thorax, stomach, and colon gave negative results. The blood count disclosed slight secondary anemia. The Wassermann reaction of the blood was negative. Following is the proctoscopic report: "The middle third of the rectum is the site of scarring and puckering of the mucosa with a small degree of contraction of the lumen. There are several large, superficial ulcers in the healing stage."

A diagnosis was made of an inflammatory rectal lesion of unknown etiology. Local treatments, daily hot irrigations, and administration of tincture of iodine by mouth were advised. After a month's treatment the final examination revealed only scarring at the site of the original inflammatory area. The patient was advised to continue the hot irrigations and to return in three months for examination. Attention to the constipation was urged and efforts to correct it by dietary measures also were carried out. The constipation probably explains the epigastric distress, since relief is afforded by movement of the bowels.

Bleeding from the bowel is always a symptom of primary importance, and almost the first thing to settle is the problem of malignancy. I would feel that the exploratory operation undertaken at the onset of the bleeding was a correct procedure. There might well have been a very small, early carcinoma. Of course, this advice hinges on the reliability of the various diagnostic procedures, but if these procedures have been carried out competently, I think exploration must be considered.

As to this particular case, the "feel" of the rectal lesion was not characteristic of malignancy although it was too high to examine carefully with the finger. As in the previous case, the etiology is uncertain. It does not seem to be that of "segmental ulcerative colitis." The fairly prompt response to nonspecific treatment would seem to rule out parasitic or tuberculous lesions. Focal infection is to be thought of, but there were no apparent foci. From the history and character of the lesion, it is not improbable that the patient may have further trouble; hence she was urged to remain under observation.

CONCLUSIONS

1. A diffuse, granular, easily bleeding rectal mucosa, together with the roentgenologic appearance of ulcerative colitis,

usually means that ulcerative colitis is present, but there are occasional cases in which this same clinical picture is produced by *Endamœba histolytica*.

2. A poor scientific procedure but a helpful clinical rule when laboratory facilities are poor is to give a therapeutic test with emetin in cases of diarrhea that do not respond to what are thought to be correct measures.

3. Rectal bleeding following the use of radium for pelvic conditions may be due to radium ulcer and not to carcinoma.

4. Rectal bleeding is probably the outstanding symptom of carcinoma in the distal portion of the large bowel; yet one must not rush to a premature conclusion that carcinoma is present.

5. Masses felt in the rectum are usually malignant, but again careful study is necessary before the patient is given an opinion.

RESULTS FOLLOWING THE KOCHER OPERATION FOR PROLAPSUS UTERI

LEDA J. STACY

ACQUIRED prolapse of the uterus occurs as a result of injury to the pelvic floor and to the cardinal ligaments of the uterus which allow the organ to become retroverted. When the uterus is in the retroverted position, intra-abdominal pressure forces it downward in direct line with the outlet of the pelvis; if the perineal support is inadequate, the uterus in time protrudes from the vagina and may or may not carry the bladder and rectum with it in the downward course.

Since Hippocrates first mentioned prolapsus uteri and described a wooden pessary, many operations have been devised to restore the uterus to its normal anterior position in the pelvis and to correct the prolapse of the bladder and rectum. Kocher advocated fixation of the body of the uterus into the abdominal wall, and John B. Murphy described a modification of the Kocher operation. In this modified operation the uterus is split, a portion of the fundus is removed, and the remaining two flaps of the uterus are fastened to the external surface of the rectus abdominis muscles.

There is a small group of patients in whom the Kocher operation is indicated, although from the dearth of reports in the literature it is evidently seldom used. In older women who have had partial or complete prolapse of the uterus for a long time with so much relaxation of all the supports that nothing less than vaginal hysterectomy and obliteration of the vagina will correct the displacement, the operation overcomes the prolapse and leaves an adequate vagina, and in women who are in poor condition for more radical treatment, the operation is done easily and with safety. Theoretically, the perineal support should be

restored at the same time or immediately after elevation of the uterus. A review of the results following the operation at The Mayo Clinic shows that relief of symptoms occurred in a larger percentage of the cases in which the combined operation was done.

From 1912 to 1925, inclusive, the Kocher operation was performed in eighty-two cases and without operative mortality. Five patients have died subsequently. One died of "rheumatism" at the age of sixty-eight years, five years after the operation and without return of pelvic symptoms; one was treated at the clinic seven years after operation for carcinoma of the cervix and died later of the malignant condition. Three patients were reported to be "deceased"; one of these had returned five years after operation for repair of a ventral hernia at which time there were no pelvic symptoms. Five patients had had abdominal supravaginal hysterectomy for prolapse previously, but are included in this series because the cervix was brought up and fastened to the rectus abdominis muscle, although in such cases it is sometimes difficult to obtain a satisfactory attachment.

In twenty-eight patients the perineum was repaired at the time of the Kocher operation or a few days afterward. In this group, nine patients had had operations for prolapse previously, two had had abdominal supravaginal hysterectomy, three had had shortening of the ligaments, two had had perineorrhaphy, one patient had had a Baldy-Webster operation, and one patient had had ventrosuspension. In this group of twenty-eight patients, nineteen have been heard from. One patient died; the cause of death was not reported.

Of the eighteen patients who are living, thirteen (72.2 per cent) were completely relieved and five (27.7 per cent) were partially relieved of symptoms. Of the five patients who were partially relieved, one patient returned because of recurring cystocele which was relieved following a Bovee operation; this was the only patient who had a subsequent operation for relief of recurring symptoms. Two of the five patients had postoperative ventral hernia. Eleven of these eighteen patients had had symptoms referable to the bladder previous to operation and all

but two were completely relieved after operation. It is interesting that two patients who had not had frequent micturition before operation complained of it subsequently; one of these had incontinence.

In fifty-four patients the abdominal operation only was done but most of these patients were advised to return later for perineorrhaphy and failed to do so. Of the fifty-four patients, forty have been heard from. Three of the group of fifty-four patients had had abdominal subtotal or supravaginal hysterectomy previously, eight had had perineorrhaphy, six had had shortening of the ligaments, and two had had amputation of the cervix. In the group of forty patients who have been heard from, twenty-one (52.5 per cent) reported entire relief of symptoms, thirteen (32.5 per cent) reported partial relief of symptoms, and six (15 per cent) were not improved. Four patients returned for subsequent operations: one patient had a Bovee operation for cystocele, one had hysterectomy, one had an operation for a high rectocele, and one had perineorrhaphy and an operation for a vaginal hernia. In one case in which abdominal supravaginal hysterectomy had been done elsewhere previous to the Kocher method of fixing the cervix into the abdominal wall, operation was performed subsequently elsewhere for recurring cystocele. In the group of forty patients there were four patients who had postoperative ventral hernia; the patients were obese and the condition of the wall of the abdomen was poor.

Thirty-four of the forty patients had had symptoms referable to the bladder before operation; twenty-four of these patients (70.7 per cent) were relieved, nine continued to have some bladder irritation and one patient had incontinence. Four patients who did not have bladder trouble previous to operation reported trouble afterward, described in most instances as "frequency."

It is advisable in any case in which the uterus has been completely prolapsed for some time to keep the patient in bed with the uterus replaced for a few days before the operation. Patients in whom the cervix has been exposed for a long time and has become ulcerated should be put to bed, the uterus returned

to place and the cervix treated with medicated lamb's wool tampons until the ulcer has healed before the operation is done.

CONCLUSIONS

In carefully selected cases the Kocher operation for prolapse of the uterus and for cystocele gives relief of symptoms and leaves a normal vagina. It is a comparatively safe operation in patients who are poor surgical risks for other types of operation. Perineorrhaphy should be done immediately following the abdominal operation; the statistics at the clinic show that complete relief of symptoms was obtained in 72.2 per cent of the cases in which perineorrhaphy was done, as compared with 52.5 per cent in the cases in which the perineum was not repaired.

SEVERE CHRONIC RENAL INSUFFICIENCY: THREE CASES OF DIFFUSE NEPHRITIS OF LONG DURATION

E. G. Wakefield and Norman M. Keith

Of the prognostic criteria in chronic renal insufficiency, the concentration of creatinine in the blood is undoubtedly the most valuable. A concentration of creatinine of more than 2 mg. in each 100 c.c. of blood may be considered of grave prognostic significance in chronic glomerulonephritis. This is true because the concentration of creatinine in the blood is relatively unaffected by the diet and is the last of the nitrogenous bodies to accumulate in the blood. On the other hand, the prognostic value of concentrations of creatinine is dependent in part on the type of renal lesion present. It is a recognized fact that in acute nephritis, polycystic kidneys, and the types of chronic diffuse nephritis reported here, long standing or transient, increases in concentration of creatinine in the blood do not have the same prognostic value as in chronic glomerulonephritis.

In this report we are presenting three cases of renal insufficiency of long duration. Without marked disability these patients lived from two to seven years with concentrations of creatinine of from 2.3 to 5.8 mg. in each 100 c.c. of blood.

REPORT OF CASES

Case I.—A man came to the clinic in January, 1916, at which time he was thirty-five years of age. His chief complaint was "lumbago," described as a pain in the lower part of the back, which had been present two or three years, and which was made worse by motion. He also complained of burning sensations in the interscapular region, which he had had for about five or six months. At times he had had dizzy spells lasting only a few minutes.

On examination the pupils were found to be large, but they responded to light. The deep reflexes were normal. Heart and lungs were not unusual and the blood pressures were systolic 140 and diastolic 85, measured in millim-

eters of mercury. The edge of the liver was palpable. The ophthalmoscopic examination did not disclose anything of importance. The Wassermann reaction of the blood was positive and that of the spinal fluid, negative. A diagnosis of syphilis was made. Detailed study of the cardiovascular-renal status was not made (Table 1).

The patient returned to the clinic in 1918, complaining of double vision. About two months prior to this second admission, ptosis of the right upper lid had been noted and lasted about a month. As soon as the ptosis had begun to disappear, the double vision had begun. There was only a slight direct light reflex and a fair convergence reflex; on ophthalmoscopic examination the media was clear; the head of the left optic nerve was slightly hyperemic, and there were coarse, granular, pigmentary changes in the macular region of the left eye. Neurologic examination disclosed absence of knee and ankle jerks. A diagnosis of tabes dorsalis was made. The patient had received antisyphilitic treatment during the interval between his visits of 1916 and 1918, and some of the subjective symptoms of which he had complained in 1916 had improved.

In 1927 the patient again came to the clinic because of severe pruritus of the legs and pain in the back between the shoulders. The prutitus had started six or seven months before admission and was always worse at night, often preventing his going to sleep. There was pain in the back and between the shoulders which came on now and then, especially when he was tired. He had no other complaints. On general examination it was found that the pupils reacted to accommodation but not to light. Examination of the fundi was essentially negative. There was marked dental sepsis. The lymph nodes were enlarged in the neck, and the thyroid gland was palpable. Examination of the thorax disclosed that the heart was somewhat enlarged and that the sounds were regular in rate and rhythm. Knee and ankle jerks were absent, but there was no Babinski reflex. The reflexes in the upper extremities were diminished. We also thought that there was slight disturbance of cutaneous sensation in the lower extremities.

The patient returned for reëxamination in January, 1928, reporting some improvement during the last year. He had had no antisyphilitic treatment in that time. Two or three weeks prior to admission he had had some occipital headaches on arising in the morning, but these had passed off as soon as he was up and about. He also had had nocturia during the last year. He still complained of pain between the shoulders and in the legs, although it had become no worse. General examination disclosed slight cyanosis of the lips and Argyll-Robertson pupils. The heart was 13 cm. to the left, 3 cm. to the right, and there were no definite murmurs. The aortic second sound was greater than the pulmonary second sound. The blood pressures were systolic 190, and diastolic 100. The lungs were clear. There was absence of knee and ankle jerks. A day or two after the patient reported at the clinic he had an acute illness with fever and a sudden rise in blood urea and creatinine. This attack slowly subsided after treatment, which included intravenous administration of glucose.

The patient was readmitted to the clinic in June, 1929, complaining of weakness. There was general anasarca, and the heart was enlarged, although

TABLE 1

CLINICAL AND LABORATORY DATA IN CASE I

Date of remission.	Blood pressure.		Blood.					Urine.						
										Graded 1 to 4.				
	Systolic.	Diastolic.	Wassermann.	Urea, mg. in each 100 c.c.	Creatinine, mg. in each 100 c.c.	Erythrocytes, millions.	Hemoglobin, per cent (Dare).	Specific gravity.	Reaction.	Albumin.	Casts.	Pus.	Erythrocytes.	Phenolsulphonephthalein, per cent excretion.
January, 1916	140	85	++++					1.017	Acid.	2	2	2	0	
February, 1927	154 180	100 100	0	56 72	3.5 3.7	4.00 3.95	72 70	1.013 1.017	Acid. Acid.	2 2	0 Occasional.	0 Occasional.	0 0	25
January, 1928.	175 125 155	100 70 90	0	72 165 256 241 113 88	4.2 8.3 12.6 11.6 3.5 3.5	4.30 4.11	75 71	1.008 1.015 1.015 1.005	Acid. Acid. Acid. Acid.	3 1 2 1		4 3 4 3	Occasional.	15
June, 1929.	185	110	0	318	13.2			1.012	Acid.	4	Occasional.	2		

Patient died July, 1929.

the sounds were regular. There were signs of marked pericarditis and of some free fluid in the thorax on both sides. He had some ascites. Blood pressures were 185 systolic and 110 diastolic. The Wassermann reaction of the blood was negative. The status of renal function is given in Table 1. The patient was dismissed June 14, 1929, with a hopeless prognosis and a diagnosis of chronic pyelonephritis, chronic diffuse nephritis with pericarditis, and uremia (Table 1).

A man, who was first seen in 1916, when he was aged thirty-five years, had syphilis. At that time he had albumin, pus, and casts in the urine and a blood pressure certainly at the upper limits of normal for a man of his age. Antisyphilitic treatment was given between 1916 and 1918 without apparent harm. By 1927 (eleven years later) the renal disease had definitely progressed and marked renal insufficiency was evident; the blood pressure was definitely elevated and the concentration of blood creatinine was 3.5 and 3.7 mg. in each 100 c.c. In 1928 he had an acute exacerbation of the renal disease, with marked retention of urea and creatinine, but his condition improved and subjectively he seemed none the worse off afterward. He lived fairly comfortably for eighteen more months before he returned in his last illness. The diagnosis was chronic pyelonephritis, chronic diffuse nephritis, and generalized arteriosclerosis with hypertension.

Case II.—A man was admitted to the clinic in July, 1922, when he was fifty-five years of age. He gave a history of having had typhoid fever at the age of twenty-eight years, and said that he had often had attacks of acute infection in the upper part of the respiratory tract. The patient came to the clinic complaining of "Bright's disease." His symptomatic complaints were occasional headaches and a "tired and rundown feeling." The illness had begun in 1921 with an attack of fever, chills, and cold in the head similar to the attacks which he had had in the past, but this time the attack had not "worn off" in two or three days. It had persisted for about three months, although the fever had subsided within a short time after onset. In the early part of his illness a dull aching occipital headache and swelling of the feet and legs had developed. At times he had felt nauseated and often had induced vomiting for relief. He had become very weak. His urine had been examined early in the illness and had been found to contain "abundant albumin." After two or three months he had recovered from this attack and had returned to work feeling well. However, since that time he had had occasional headaches and he has been obliged to urinate two or three times a night.

In April, 1922, the patient had had a second attack of "cold and cough," during which he had been confined to bed for two months. Some fever had occurred during the first month. The headaches had become much worse and his feet and legs again had become swollen. There had been some dyspnea on exertion; he had been nauseated at times, and he had felt very weak. Hemorrhoids also had caused him considerable distress at this time. During a period of three or four days in the early part of his illness he had passed bright red blood in the urine, and had not been able to be up and about until June, 1922. At that time he had noticed that his vision was poor, but it had shown some improvement before his admission. He also felt that his hearing had become impaired during the year before we saw him. His normal weight was 156 pounds, but at the time of his admission it was 139 pounds.

The pupils reacted poorly to light. Examination of the fundi showed some blurring of the margins of the disks and the vessels were slightly tortuous. In the left half of the retina, in the region of the disk, were many old scars. Many of the teeth had been extracted, but those which remained were in fair condition. There were some palpable lymph nodes in the right anterior cervical triangle. Examination of the heart disclosed little except a soft, systolic murmur at the apex, with the second aortic sound accentuated and greater than the pulmonic second sound. The blood pressure was increased to 200 systolic and 110 diastolic. The lungs were clear and the abdomen was apparently normal. There was peripheral sclerosis of the brachial and radial arteries, graded 3. There was no edema and the reflexes were active. Rectal examination disclosed a few hemorrhoidal tags; examination of the prostate gland gave essentially negative results. Appropriate studies indicated that there was distinct impairment of renal function (Table 2). After more than a week in the hospital the patient was dismissed with the diagnosis of chronic renal arteriosclerosis, with renal insufficiency, generalized arteriosclerosis and hypertension.

The patient returned in July, 1923, with the report that during the last year his health had, in general, been very good. He had had no untoward symptoms and had been able to carry on his work. His weight had remained satisfactory. On general examination the blood pressures were found to be 170 systolic and 110 diastolic. The lungs were clear except for slight emphysema. The heart was 10 cm. to the left and 3 cm. to the right; the sounds were slightly distant, but regular and with no murmurs. There was sclerosis of the brachial arteries, graded 3. Nothing abnormal was found in the abdomen except relaxed inguinal rings. There was slight enlargement of the prostate gland, but it was not tender. Reflexes were active and equal, and there was no edema. Examination of the fundi gave essentially the same results as on the previous admission. The patient's condition was considered stationary. If anything, the process in the retinal vessels was subsiding. The diagnosis on dismissal, at the end of the second period of observation, was the same as that made at the end of the first visit. In November, 1929, this patient was carrying on his work about as usual and was feeling well. About the middle of November he became ill and he died December 2, 1929 (Table 2).

TABLE 2

CLINICAL AND LABORATORY DATA IN CASE II

Date of admission.	Blood pressure.		Blood.					Urine.					
	Systolic.	Diastolic.	Wassermann.	Urea, mg. in each 100 c.c.	Creatinine, mg. in each 100 c.c.	Erythrocytes, millions.	Hemoglobin, per cent (Dare).	Specific gravity.	Reaction.	Graded 1 to 4. Albumin.	Graded 1 to 4. Casts.	Graded 1 to 4. Pus.	Phenolsulphonephthalein, per cent excretion.
July, 1922.	200 130	110 85	0	52 65 51 37	 2.3 2.2 2.2		74	1.014	Acid.	3	1	1	20
July, 1923.	170	110	0	46	2.2	4.70	78	1.020	Acid.	3	2	1	30

Patient active and comfortable until shortly before his death, December 2, 1929.

In 1922, when a man aged fifty-five years was first seen, his urine contained albumin, pus, and casts. The blood pressure was elevated, but fell markedly after rest. There was definite, marked, renal insufficiency. Examination of the vessels of the retina disclosed some sclerosis and there were scars in the left retina. One year later there was no further progress of his renal disease. He lived until December 2, 1929, and until a few weeks before his death he was active physically. The diagnosis was chronic renal arteriosclerosis with renal insufficiency and generalized arteriosclerosis with hypertension.

Case III.—A man aged forty-seven years who had had good health in the past, on admission to the clinic in January, 1924, complained of bladder trouble. He said he had had nocturia for two years, with bed wetting. For eighteen months he had drawn his urine twice daily with a catheter. Residual urine had been found in 1920. On admission to the clinic he appeared to be well developed and well nourished. Ophthalmoscopic examination gave negative results. The pupils reacted normally. His heart was normal in size and there were no murmurs. Roentgenologic examination of the kidney, ureters, and bladder, and cystoscopic examination, did not reveal abnormality. Roentgenologic examination of the teeth disclosed three teeth with periapical infection. There was no definite evidence of disease of the central nervous system. The diagnosis at this time was chronic pyelonephritis with renal insufficiency, generalized arteriosclerosis, and benign hypertension.

On the patient's return in August, 1926, he said he had done very well at home and had continued using the catheter two to three times daily. He

had gained about 40 pounds in weight. Five weeks before he came to the clinic the second time a cold had developed; he had had fever and difficulty in passing the catheter. His home doctor had advised prostatectomy. On admission to the clinic this time he was well developed and obese. The prostate gland was shown to be somewhat enlarged. Roentgenologic examination of the kidneys and ureters gave negative results. A cystogram gave evidence of a cone-shaped bladder. Electrocardiographic studies and ophthalmoscopic examination did not reveal abnormality. Results of laboratory studies are shown in Table 3. The prostate gland was removed.

The patient returned in October, 1927, when he stated that he had been able to do considerable work and had done well until August, 1927. He complained of headaches and dizzy spells and that he often became weak. These troubles were severe enough to incapacitate him. His heart measured 14 cm. to the left and 3 cm. to the right; there was a soft, basal systolic murmur and sclerosis of the brachial arteries, graded 2. Examination of the fundi revealed sclerosis of the retinal arteries, graded 1. Roentgenologic examination of the kidneys, ureters, and bladder gave negative results. He was dismissed after ten days of observation with the same diagnosis that had been given on previous visits, except that arteriosclerosis and hypertension were more advanced.

The patient returned in May, 1929. He had done fairly well in the interval and had been able to work a little, although he had had frequent frontal headaches and had been somewhat weak. About a week before this visit to the clinic he had had hematuria, "urine red with blood," and during the week or ten days before we saw him he had moderate nocturia. There was little change in his condition from that of his last visit. Examination of fundi revealed sclerosis, graded 2, with hemorrhages and exudates, the usual picture of the retinitis of benign hypertension. Roentgenologic studies of the kidneys, ureters, and bladder, and of the thorax, gave negative results. Electrocardiographic tracings disclosed inverted T waves in leads II and III. Cystoscopic examination showed that the blood was coming from the right kidney. There was good evidence that the left kidney was not functioning. The patient was sent home with a guarded prognosis. He was alive in December, 1929 (Table 3).

The patient, a man aged forty-seven years, was first seen in January, 1924. Four years before he came to the clinic residual urine had been found. At the time of his admission the blood pressure was elevated, there was generalized arteriosclerosis, slight anemia, and marked renal insufficiency. The concentration of blood urea and of creatinine were greatly increased: respectively, 130 mg. and 5.8 mg. in each 100 c.c. of blood. There was little demonstrable progress in the renal insufficiency by 1926. At this time he underwent prostatectomy, from which he recovered. The concentration of blood creatinine remained

TABLE 3

Clinical and Laboratory Data in Case 3

Date of admission.	Blood pressure.		Blood.						Urine.						
	Systolic.	Diastolic.	Wassermann.	Urea, mg. in each 100 c.c.	Creatinine, mg. in each 100 c.c.	Erythrocytes, millions.	Hemoglobin, per cent (Dare).	Leukocytes, thousands.	Specific gravity.	Reaction.	Graded 1 to 4.				Phenolsulphonephthalein, per cent excretion.
											Albumin.	Casts.	Pus.	Erythrocytes.	
1/26/24	140 160	90 85	0 0	130 119	5.8 8.9	3.64 3.40	60 66	2,000 16,000	1.010 1.006	Acid. Acid.	2 1	0 0	0 3	0 0	 10
8/30/26 Prostatectomy.	180	110	0	58 88 102 182 70	 2.6 3.5 7.6	4.58	76	8,000	1.011	Acid.	3	0	4	1	Faint return.
10/17/27	185 175	100 100	0	80 82 56	 5.0 3.5	 6.5 5.1			1.010 1.014	Acid. Acid.	2 1	0 0	4 1	0 0	15
5/22/29	210 200	120 115	0	94 68 63	4.6 9.7 6.2	4.41	76	6,900	1.010	Acid.	4	0	3	0	10 5

Patient's condition stationary.

high. By this time the blood pressure was somewhat more elevated. In 1927 there was very little evidence of further progression of the disease process. The patient was definitely worse in 1929, although he was remarkably well considering the length of his illness. He had shown persistent concentration of blood creatinine of more than 5 mg. in each 100 c.c. for six years and was still living and doing fairly well. The diagnosis was chronic pyelonephritis with renal insufficiency, general arteriosclerosis and hypertension.

SUMMARY

The first patient lived two years and six months after the concentration of creatinine in the blood was 3.5 mg. in each 100 c.c., and eighteen months after an acute exacerbation of his renal disease, during which a concentration of creatinine of 12.6 mg. in each 100 c.c. was observed. The second patient lived seven years and five months after a concentration of blood creatinine of 2.3 mg. in each 100 c.c. was observed. The third patient is still living, six years after a concentration of blood creatinine of 5.8 mg. in each 100 c.c. was first observed. There could be much speculation as to whether this patient had a lesion of the kidney in addition to his bladder trouble before he began to use the catheter. One could also speculate as to whether the prostatic hypertrophy with subsequent pyelitis was the primary reason for the renal insufficiency, which he undoubtedly had when he first came to the clinic.

It is important to emphasize that the renal lesion present in these three cases was of the mixed type and not that typical of chronic glomerulonephritis. Severe, chronic renal insufficiency due to diffuse nephritis has been shown to exist for periods of six to seven years. Even acute exacerbations of the renal disease may occur during this period, with subsequent partial recovery. Clinical observation reveals the fact that the patient's disability may not be marked nor prevent his carrying on his usual work.

INTERSTITIAL CYSTITIS: ITS TREATMENT BY OVERDISTENTION OF THE BLADDER*

HERMON C. BUMPUS, JR.

IN 1914 Hunner described a new urinary disease characterized by all the symptoms of the most severe cystitis; the frequency which made it necessary to pass urine as often as every fifteen or twenty minutes was associated with extreme dysuria. The unusual thing about the disease was that in the presence of severe symptoms of cystitis analysis of urine usually gave negative results and cystoscopic examination revealed only insignificant pathologic changes characterized by areas of scarring in the mucosa. If the bladder was overdistended, the mucosa would bleed rather freely. Such overdistention, as well as the touching with the cystoscope of these areas, was associated with extreme pain.

For lack of a better name, Hunner referred to these lesions as a "rare form of bladder ulcer." Cullen, later, because of the difficulty of diagnosis, offered the term "elusive ulcer," Geraghty called it "paracystitis," and Keene referred to it in his reported cases as "pan-mural ulcerative cystitis." Braasch suggested the term "submucous ulcer" because the pathologic process, consisting of infiltration with round cells and other evidences of an infectious process, is mainly below the mucosa.

As knowledge of the disease has grown, it has become apparent that the areas are frequently very extensive and not localized to any one portion of the wall of the bladder. Therefore at The Mayo Clinic the term "interstitial cystitis" has come to replace the term "submucous ulcer."

* Read before the North Central Branch of the American Urological Association at the sixth annual meeting, Rochester, Minnesota, November 21 and 22, 1929.

The disease was thought by Hunner to be of focal origin, and this suspicion was confirmed by the experimental work of Bumpus and Meisser. We produced the ulcer experimentally, in animals, with organisms obtained from the teeth and tonsils of patients with the disease. Although cases in the male have been reported, the disease seems to be far more common in the female. This is probably due to infection about the cervix acting as a focus, or to direct extension of infection from the cervix, for Moench and Counseller, of the clinic, have reproduced the condition by injecting into laboratory animals organisms obtained by swabbing the cervix of a woman with the disease.

There is also a very noticeable incidence of previous pelvic operations, especially of hysterectomy, among the women who suffer from interstitial cystitis. Presumably the infection about the cervix becomes active at the time of operation and invades the wall of the bladder, for I have seen numerous cases in which there has been extensive involvement of the bladder dating from a short time after previous pelvic operation.

In his original work Hunner recommended resection of the involved portion of the bladder, and this method was followed by others, notably, Kretschmer, Keene, and Reed, all of whom reported good results. However, Hunt, in 1921, called attention to the fact that these reports were all made a comparatively short time after operation and that in his experience the results, after several years, were not as good as the immediate results; since that time surgical removal of the involved wall of the bladder has not been popular.

Seeking some other method of treatment, gratifying results followed fulguration, and this procedure immediately became popular, as it gave almost immediate relief in many cases. Patients who had voided as frequently as every twenty to thirty minutes would find themselves sleeping uninterruptedly the night following such treatment.

After this procedure had been employed in a large series of cases, it became apparent that the disease, as in cases in which operation had been done, tended to recur and that subsequent fulguration was necessary. I was so unfortunate as to en-

counter a case in which the involved area had been treated by electrocoagulation three times during the previous two years. Following the same treatment for the fourth time, although care had been taken not to desiccate too deeply, the area became gangrenous because of destruction of blood supply by the previous electrocoagulation, and death from peritonitis followed.

Because of this occurrence I sought some other means of treatment. Frontz had suggested that hydraulic overdistention of the bladder was of use in comparatively superficial cases. Kretschmer took exception to this because in his experience severe pain had followed. I applied the procedure under a general anesthetic and obtained most gratifying results, although I do not pretend that cure has been accomplished. Depending on the extent of involvement, there is improvement in symptoms, varying in duration from a few months to years in occasional cases. As the method is simple, there is no contraindication to its frequent repetition and the relief produced is enough to make the sufferer grateful even if complete cure does not result.

With an irrigating cystoscope the bladder is allowed to distend to as great a volume as the pressure exerted by approximately 120 mm. of mercury will permit. Such a pressure is obtained by having the irrigating reservoir about four feet above the patient. At the time of overdistention, the involved areas usually bleed rather freely, but in only one case of considerably more than 100 cases has any serious complication resulted. In this case the area of scarring tore for approximately 2 cm. and a perivesical abscess resulted. This drained into the bladder and the patient made a satisfactory recovery. I believe such an accident is the only associated danger if care is taken not to exert too great pressure at the initial treatment.

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THE COURSE AND PROGNOSIS IN CHRONIC INFECTIOUS ARTHRITIS: A STUDY OF RELAPSES

DAVID G. GHRIST AND PHILIP S. HENCH

A FREQUENT and anxious query of patients with arthritis is as follows: "After a period of treatment I am now better. How can I maintain and increase this improvement? If I continue treatment faithfully can I expect this improvement to continue without interruption?"

The clinical course of cases of infectious (nonspecific) arthritis may vary so greatly that answer to this query must be made with caution. When observation covers weeks or months, it is perhaps possible to venture a prognosis concerning the outcome and permissible, for encouragement of optimism on the part of

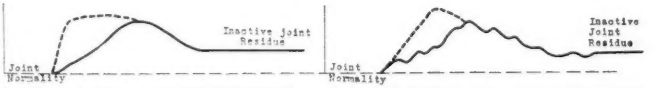

FIG. 239.—The course of nonspecific infectious arthritis.

the patient, for the physician to speculate as to whether the peak of activity has been reached or whether the fire is burning out.

One of the discouraging features in the treatment of arthritis is the fact that a patient who is responding well to treatment, suddenly, and often without any obvious reason, will have a relapse of varying intensity. These exacerbations tax to the utmost the confidence of both physician and patient in the efficacy of the treatment being used, and constitute one of the major reasons why treatment of merit is abandoned prematurely.

CAUSES OF EXACERBATIONS OF CHRONIC INFECTIOUS ARTHRITIS: THE EXPERIENCE OF THIRTY-FIVE PATIENTS

Classification of causal factor according to questions asked the patients.	Patients who experienced exacerbation. Grade. 1	2	3	4	Total.
Physical:					
Excess of normal physical activity	8	15	1		24
Acute superimposed injury	1	3			4
Prolonged maintenance of one posture	4	14	1*		19
Increased pain after physiotherapy: diathermy, baking		2			2
Increased pain after treatment by radium or roentgen ray					
Total					49
Weather:					
Change to cold weather		8			8
Proximity of storm	5	9†	5		19
Rainy or damp (not especially cold) weather	3	9			12
Geographic changes: moving to cold climate	1				1
Total					40
Sudden exposure:					
Cold drafts; change of temperature	6	6			12
Cold bath, or swimming in cold water	1	1	1		3
Drenching by rain or dampness		7	1		8
Total					23
Diet:					
Irregularity in hours	4				4
Influence of meat and protein	2				2
Influence of carbohydrates (starches)	1	1			2
Influence of fats					
Change from diet low in calories to one high in calories or heavy meal	1	3			4
Special idiosyncrasy (eggs, cantaloupe, oranges, or tomatoes)	4	1			5
Alcohol	1				1
Total					18
Intestinal influence:					
Prolonged constipation (no bowel movement in two or three days, or more)	4	11	7		22
Diarrhea, at least two days					
Total					22
Mental strain:					
Mental fatigue from excessive normal mental activity					
Abnormal mental fatigue: worry, anxiety	4	7	1		12
Acute mental fatigue: nervous shock		2			2
Total					14
Hygiene:					
Lack of outdoor sunshine and air	9	1			10
Lack of sleep or irregular sleep	6	9			15
Total					25
Infection:					
Removal of foci, including abdominal foci	1	3	5	1	10
Intercurrent infections	2	10	4		16
Total					26
Endocrine:					
Just before menstruation	1	3			4
During menstruation			1		1
Just after menstruation		1			1
Menopause		2			2
Thyroid abnormality		1			1
Pregnancy; miscarriage		4			4
Total					13

* Exacerbation of one week's duration after sleeping in cramped position for four or five hours.
† Pain often relieved within few minutes after beginning of storm.

Although some cases of infectious arthritis may start acutely, may become subacute, and gradually, after a period of chronicity, may subside, with little, if any, interruption in the course (Fig. 239, A), usually there are numerous phases of increased and decreased activity in the inflammation. In a large percentage of patients the period of chronicity does not constitute an unwavering decline in activity, but the periods of improvement frequently are rudely punctuated by exacerbation in old regions of involvement and the appearance of involvement of new regions. This occurs not only in cases in which treatment is carried out in a haphazard manner, but even in spite of uninterrupted therapeutic endeavor. In a consideration of the immediate prognosis, therefore, it is necessary to picture the possibility of such a course as that shown in Figure 239, B, and to urge continuation of treatment in spite of peaks of renewed activity. Yet, it may be entirely justifiable to predict hopefully an ultimate favorable prognosis in spite of them.

What are the causes of such relapses, and can they be avoided or modified? The data herein reported represent an informal clinic on relapses, as illustrated by the reported experiences of the thirty-five patients who, November 1, 1929, were on the arthritic service at The Mayo Clinic. None had enjoyed long, uninterrupted periods of improvement previous to admission. Although they constitute only a very small series, it was felt that their experiences with the disease should be considered fairly representative, inasmuch as the average duration of the arthritis was six years. In addition, the follow-up letters of a very large group of patients heretofore dismissed from the clinic indicate that misadventures similar to theirs are the common lot prior to the ultimate inactivity of the disease.

EXCITING CAUSES AT ONSET OF ARTHRITIS

One causal factor alone probably only rarely institutes arthritis, no matter what is the main cause, unless it is in the case of gross, extensive trauma. One of the functions of joints is to accept a considerable amount of physiologic trauma. Because of this ever-present factor, probably every case of infec-

tious, degenerative or chemical arthritis is in varying degrees influenced in onset and localization by trauma. Still, back of trauma and infection as chief inciting and predisposing causes, lies "rheumatic diathesis," which can perhaps be defined as a deficiency in the inherited and acquired defensive mechanism against infection of the body in general, and of the joints in particular, to withstand the offensive forces of the four major causes of all arthritis: infection, degeneration (senescence), trauma, and alteration in the chemical constituents of the body. The predisposing and precipitating causes of infectious arthritis listed by most authors include in general the following:

The predisposing factors are infections and miscellaneous factors. The infections include pleurisy, influenza, scarlet fever, rheumatic fever, gastritis, puerperal fever, malaria, dyspepsia, erysipelas, osteomyelitis, boils, dysentery, and mucous colitis. The miscellaneous factors include physical strain, fatigue, mental strain (worry), vaccination, arteriosclerosis, and underweight.

The precipitating causes are "endocrine" factors, infections, and miscellaneous factors. The endocrine factors include natural menopause, artificial menopause, pregnancy, dysmenorrhea, and increased or decreased activity of the thyroid gland. The infections include influenza, pneumonia, infections of the throat, gonorrhea and chorea. The miscellaneous factors include exposure (storms, wet feet, and damp cellars), physical excess, deficient muscular exercise, war gas (in soldiers), anemia, varicose veins, operations, "alimentary" causes (including postoperative, forced convalescent diets), mental strain, sacro-iliac strain, urticaria (hay-fever), treatment by vaccine, and the use of radium.

The foregoing summary of the factors involved includes those stipulated by Longstreth, Garrod, Banatyne, R. Llewellyn Jones, Llewellyn and Jones, Thomson and Gordon, Strangeway's Cambridge Committee, Stockman, Osler, McCrae, Barker, Crowe, Futcher, Fischer, Van Bremen, Glover, Pemberton, Cecil and Thompson.

It would be reasonable to expect that the exciting causes of the relapses would be about the same as those of the initial onset,

and that the causes that originally accumulated to break joint compensation for infection are the same that may repeatedly cause subsequent breaks in a compensation that is in process of being established by treatment. On careful special questioning of our patients they offered the following causes for their relapses, which they felt to be definite and based on repeated observations (tabulation).[1]

The insults in general instigated four types of unfavorable reactions: Grade 1, temporary discomfort of very mild degree, lasting at most a few hours, with increase of arthritic symptoms, but little, if any, increase in objective signs; grade 2, minor but definite exacerbations associated with definite increase of signs and symptoms lasting a few hours to a few days; grade 3, major exacerbations, with increase of subjective and objective phenomena severe enough to change the status of the patient from fairly comfortable to miserable, from compensatory to decompensatory, even to the temporary status of a bed patient for a few days to two to three weeks; grade 4, serious exacerbations, more or less totally incapacitating the patient for several weeks.

PRESUMPTIVE OR ALLEGED EXACERBATING CAUSES IN PRESENT SERIES

In this series the insults leading to serious exacerbations (grade 4) were rare; in only one instance, the exacerbation came on after removal of infected teeth and confined the patient to bed for three or four weeks. Relapses of grade 3 resulted chiefly from barometric changes associated with approaching storms

[1] Twenty-five of these thirty-five patients were questioned with regard to predisposing causes of the chronic infectious arthritis. The following resulted: (1) Prolonged constipation for at least two months before onset (nine patients); (2) illness, upper and lower respiratory tract infection (eight patients); (3) exposure: *a*, to cold within forty-eight hours before onset (seven patients), and *b*, to damp and cold, within forty-eight hours before onset, (four patients); (4) physical strain, excess normal physical labor (seven patients); (5) irregular sleep or lack of sleep (six patients); (6) underweight (five patients); (7) subjectively and clinically cold extremities (five patients); (8) mental strain, financial, family, etc. (five patients); (9) dietary regimen, lack of vitamines, irregularity, or indiscretion (four patients); (10) trauma (four patients), and (11) endocrine disturbances (one patient).

(five cases); intercurrent infections, chiefly "colds" (four cases); removal of infected foci (five cases); and two or more days of uninterrupted constipation (seven cases). The chief causes of relapses of severity graded 2 were physical excess (fifteen cases); cramped or maintained posture (fourteen cases); constipation (eleven cases); intercurrent infections (ten cases); proximity of storms (nine cases), with inadequate sleep and mental fatigue definite additional but less frequent causes.

Twenty-two different factors were blamed for minor increases of discomfort graded 1; weather and hygienic deficiencies were the most common. Considering all degrees of increased discomfort, grades 1 to 4, the ten most frequent causes of joint decompensation were, in order of frequency, physical excesses; constipation; barometric changes or storms; cramped or maintained posture; intercurrent infections; inadequate sleep; exposure to cold; exposure to rain and dampness; worry, and lack of fresh air and sunshine.

None of the patients felt that all the exacerbations were induced by a single factor. Most of them were annoyed by several different factors, although in the majority of cases there was a chief irritant which was more prone than the others to produce increased disability. Individual exacerbating causes also demonstrated variable potentialities in the same patient. On different occasions, for example, the same degree of an insult would invoke different degrees of reaction.

ALLEGED EXACERBATING CAUSES REPORTED BY OTHER OBSERVERS

Few data can be found regarding the causes of relapses in arthritis, although, as has been shown, many investigators have listed the exciting causes of the initial onset. Longstreth blamed slight strains of tendons, muscles, and joints as causes of exacerbations, the severity of which might be considerably out of proportion to the degree of insult. Pemberton cited barometric changes and the reinstitution of a general diet after a diet low in carbohydrate and calories, as specific causes of relapses in his experience. Vaccines, ill-timed or of improper dosage, inaugur-

ated increase of disability in the experience of Crowe and others. Recrudescences of muscular rheumatism (fibrositis) were blamed by Llewellyn and Jones on pharyngitis, tonsillitis, and gastro-intestinal derangement, such as bouts of overeating and vinous excesses. Stockman, in similar cases, noted relapses following exposure to cold, to dampness or to winds; also, contradictorily, to moist or dry heat in some instances; in one case relapses were associated with diarrhea, and remissions or relapses were in accord with diminution or increased severity of the intestinal trouble.

DECOMPENSATING FACTORS

Physical factors.—Physical excesses certainly cause a large proportion of exacerbations. In spite of this, we support those who urge judicious and moderate physical exertion. The path of propriety in physical effort seems at times a narrow one, between the possibility of physical excess on the one hand, and insufficient use or disuse, with its atrophy and deformity, on the other. The orthopedic surgeons can best testify to the frequency and the magnitude of the latter's damage. Perhaps one of the differences between judicious and excess physical exertion for inflamed joints lies in the factor of trauma from weight-bearing. Exercises for the joints that do not entail weight-bearing are better tolerated than those that do. On physical exertion, as with physiotherapy, the patient should move the joints in spite of pain and of temporary discomfort for a short time thereafter, but when a reaction of redness, pain, and swelling occurs which lasts until the next day, moderation of such activity is imperative, particularly if the increased discomfort begins to accumulate. The type, extent, and situation of the pathologic change in the joints may suggest how much motion and which motions constitute acceptable physiologic trauma, and which excess and irritating trauma.

Thermal factors.—The majority of patients with arthritis feel better, not only with a rising barometer, but with the warmth of the summer, in tropical weather, or with the application of heat. They experience increased disability with cold and winter weather. However, exceptions to this rule are not

uncommon, and it has been noted that baking, diathermy, and hot applications occasionally consistently aggravate a case of arthritis which cool applications may relieve. In these cases alternating hot and cold applications (contrast douches, showers, and baths), or cold alone may give more relief than heat alone.

The explanation of the variable action of heat on these patients probably lies in an exaggeration of the normal individual variations in vasomotor response. We have observed one presumably normal person who, without the slightest sign of arthritis, repeatedly has definite, although temporary, arthralgia of fifteen minutes' duration in the knees after a hot bath, and at no other time. Again, one person reacts to a short, cold shower by a vigorous warm glow, whereas another reacts to a similar experience with prolonged shivering and discomfort. The specific vasomotor tone in individual patients with arthritis warrants study, particularly if the program of physiotherapy is to be long continued. Whether these individual vasomotor reactions depend on alterations in response of the skin to environment or on primary autonomic adjustment, as will be considered later under climatic influences, is unsettled. Fuller particularly expressed the belief that cold climates are not the cause of rheumatic disease; that in its acute form, at least, it is almost unknown near the poles, and that damp and variable weather are much more important than cold weather. It would seem that sudden shifts in temperature, whether up or down, are not borne as well as equable, even though fairly cold, temperatures.

An interesting variation was expressed by one patient who insisted that although his disability was never influenced by exposure to winds or to cold weather, he felt distinctly worse each day as soon as the sun went down. In addition he was made worse by rainy weather.

Influences of weather.—Phenomena of weather exert much influence on rheumatic joints. Various explanations have been given for this, and temperature variations, humidity, presence or nearness of storms, currents of wind, barometric pressure, and atmospheric electricity have all been blamed as the chief fac-

tors. In a recent survey from this clinic, Rentschler, Vanzant, and Rowntree studied a group of 367 patients on the arthritis service over a period of 365 days; they found that only 7 per cent of the patients seemed consistently unaffected by storms or other phenomena of weather. The remaining 93 per cent were definitely influenced in one of two ways: 72 per cent were improved by increase of barometric pressure; 21 per cent reacted in an opposite manner to the popular conception, that is, they were relieved when the barometer was falling. Some patients would react unfavorably with a falling barometer for a long period, and then, for a time, in an opposite way, for no known reason. Intercurrent infections and operations would serve to reverse or temporarily to obliterate these reactions.

These investigators concluded that although the barometer served as the best index of the influence of weather, it was not the sole factor, nor could its changes adequately explain entirely the influence of weather. Balfour, in 1816, expressed the belief that the influences of weather on joints took place through the lungs. Stockman expressed the belief that possibly the barometric changes increase or lessen the lymph pressure in the body and so indirectly increase or lessen the tension in the fibrous indurations. Llewellyn and Jones stated the belief that the influences of the weather take place through "invoking the endocrine sympathetic system, the intermediary mechanism whereby our ceaseless adaptations to an ever changing environment are secured," and that in rheumatic diseases there is failure in adaptive capacity, a state of endocrine autonomic imbalance which affects the vital processes of tissue oxygenation. Douthwaite concurred in these views, explaining such hypersensitivity to climatic changes on the basis of alterations of cutaneous function secondary to disturbances in the sympathetic nervous system.

The latter views are of considerable interest to us in view of the results of sympathetic ganglionectomy for arthritis observed in The Mayo Clinic. From our observations we cannot feel certain that the alterations in endocrine and autonomic functions are primary difficulties. We do agree, however, that there is often

crucial failure in the adaptive capacity, certainly of the skin, peripheral vasomotor system and joints. We shall watch with interest to see whether partial sympathetic ganglionectomy (removal of the inferior cervical and first and second thoracic ganglions, or of the second, third, and fourth lumbar ganglions, or a combination of these) will prevent permanently the exacerbations instigated by weather, and permit the onset of an uninterrupted remission until only an inactive residue remains. Experience to date seems to indicate this possibility. The first patient on whom sympathetic ganglionectomy was done three years ago, although previously she had been influenced markedly by changes in the weather, has since withstood the cold and changes of Canadian winters without the recrudescences that formerly were attributed to the weather. A few weeks of sympathetic release may be necessary before influences of weather cease in some cases, as suggested by the experience of two or three patients just dismissed after sympathetic ganglionectomy.

The experiences of the patients in our series are similar to those reported by Rentschler, Vanzant, and Rowntree. Many of the patients felt the baneful influences of approaching storms disappear within ten minutes after the storm broke and long before cessation of rain or snow. That phenomena of weather may lose their influence was demonstrated by the statement of one patient who has had arthritis for eight years; during the first two years the approach of a storm regularly initiated severe exacerbations (graded 3). This reaction has been entirely lacking for the last six years, although the arthritis continues in about equal intensity.

Intercurrent infections.—On the cardiac, diabetic, and nephritic services of the clinic a frequent observation is that the "common cold" is responsible for many "breaks" in compensation of the heart, of the pancreas, and of the kidneys. Whether the patient's difficulties are metabolic, or inflammatory and infectious, the "cold" seems to present definite difficulty, nor does it exhibit to arthritic patients the occasional graciousness of the more severe intercurrent infections, which, although they often increase, occasionally cause complete cessation of arthritic

activity. With colds it is possible that bodily resistance is lowered without adequate stimulation or response of nonspecific immunity. With intercurrent infections the stimulation of specific and nonspecific defensive forces may be so great as to prove an eventual boon to the chronic invalid, acting in the nature of nonspecific (analogous to protein) treatment. The prognosis as to whether benefit or harm will result from intercurrent infections probably depends on the degree of defensive exhaustion already present and the defensive stimulation possible.

Arthritis in one patient was definitely improved after an attack of erysipelas, whereas that of another was ameliorated, but not stopped, by therapeutic malarial inoculation. The "grippe" and "colds" were the chief intercurrent infections which here aggravated the condition of the joints.

Although at the clinic infections of sinuses of the skull rarely are found acting as foci of infection in cases of infectious arthritis, a different experience is reported from certain eastern city clinics. Doubt has been expressed by certain authors as to whether "sinusitis" and "colds" are really infections. Persons who are repeatedly affected by vasomotor rhinitis are more subject to colds than others. When one observes that such a vasomotor condition can be the cause of sharp reactions in the mucous membrane of the nose, and then considers the association of colds and exacerbations of arthritic conditions, one may feel it permissible to speculate on the possibility that some of these reactions of joints also are in the nature of vasomotor arthritis, of an allergy alone, or of vasomotor or allergic insults superimposed on an already present infection. Llewellyn, for one, has expressed the belief that vasomotor arthritis is an entity. Intermittent hydrops, especially, presents itself for such speculation.

Posture.—A common symptom in arthritis, periarthritis, or muscular rheumatism is marked stiffness and pain when the patient awakens in the morning, after a recumbent posture has been maintained in repose. Some of these patients experience such stiffness after even shorter periods in normal positions, such as an hour or two in the theater or in church, or even fifteen minutes in a chair. If the posture is at all abnormal or cramped,

the discomfort comes on sooner and more readily. It is noteworthy that several patients had definite, although minor, exacerbations following such temporary inactivity and in one instance marked recrudescence of disability in the joints was instigated by several hours' maintenance of a cramped position of the lower extremities during sleep. A lag in the circulation of the joints and muscles dependent on inactivity is generally blamed for the subsequent increase in discomfort. The underlying alteration in the chemical constituents of the tissue is not known, but has been thought to be one of suboxidation and partial tissue narcosis. At any rate it emphasizes the dictum: "Motion is life for the arthritic patient" and is one of the reasons why early morning physiotherapy is necessary for many to "limber up the joints."

Attention to studies on the physiology of sleep may give a clue to the cause of increased pain in the early morning. During sleep there are reductions in basal metabolism, alterations in vasomotor tone, and reduction in blood pressure, all considered potential factors in changing the sensory phenomena of inflamed joints. It may be that the biologic variations which occur during sleep, as part of the cycle of day and night, are, to a lesser degree perhaps, the same as the majority of those attending the monthly cycle in women, which is attended by menstrual arthritic exacerbations.

Constipation and dietary irregularities.—Many patients believe their arthritis to be definitely aggravated either by constipation (relieved by salts, enemas, or irrigations) or by excesses in meats, sweets, or "acid" fruits, and vegetables, for example, tomatoes. Some patients feel worse with excesses of all proteins or all carbohydrates, whereas others say they can eat several forms of proteins or sugars with impunity, but blame another form for subsequent ill-feeling. Although a few patients felt more pain in the joints after heavy meals, one patient said his arthritis felt repeatedly better after a large intake of food. The influence of constipation is far more stressed than that of any one food or group of foods. Some of these aggravations, on close inspection, seem more fancied than real; others seem defi-

nite, although difficult to explain in the light of knowledge of the part played by the intestines and foods in arthritis. Perhaps the newer suggestions of the possible part played by intestinal allergens (bacterial or from food) may be extended to the point of proof to explain what seems difficult to understand otherwise on the basis of the bacteriologic, chemical, and radiologic studies of the intestines at hand. Until knowledge is more complete, due regard must be given to those who believe in more specific dietary restrictions, notably Pemberton, or more specific intestinal therapy, among whom are Rolleston, Fishbaugh, and Fletcher. Suffice it to say that at present there seems to us to be no well-defined dietary prescriptions indicated for infectious arthritis as a disease, although we do feel that there are definite prescriptions for individual patients.

In considering diarrhea in association with exacerbations of arthritis, it must be recalled that infectious (specific?) arthritis may complicate, in 3 to 10 per cent of cases, either the dysentery caused by the Shiga bacillus, by amebæ, or by the acute and chronic ulcerative colitis associated with Bargen's diplostreptococcus. These types of arthritis seem to be closely allied to the intestinal infection and have remissions associated with the degree of activity of the dysentery. This series did not include these types.

Influence of removal of foci treatment, by vaccine, and operations.—Although removal of a focus occasionally is attended by increase in arthritis, such an event is certainly a rarity when one considers the enormous number of cases in which removal of foci is not so attended. It is much more common to hear patients say that for a few hours or days after removal of a tooth or of tonsils they had almost complete, if only temporary, relief. Certain physicians do not remove foci without making special serologic and immunologic studies of the blood (complement fixation, opsonic index, immunity titer, and so forth) to determine the proper time for their removal. Others believe that these tests give little additional data that cannot be gained from judicious regard for the patient's general resistance, based on clinical experience. It is certain that if many

foci are present their removal should be spaced judiciously and done gradually with technic that will permit little absorption. Immunologic studies which would demonstrate the optimal time for removal of foci and would indicate treatment appropriate for protection would be desirable and should be extended.

The occasional untoward reactions to vaccine and treatment with protein probably represent upsets in defensive mechanism either through immunologic processes or vasomotor alterations. One of us (Hench) studied such reactions at the clinic. The variable influences of operations act probably in a way similar to removal of foci or to development of intercurrent infections. An operation may be followed, in a case of active arthritis, by an exacerbation of symptoms in the joints. Often this may be a diphasic, protein-like reaction with a brief period of increased discomfort. Then a temporary or permanent period of relief may supervene. Occasionally patients with arthritis which has been inactive for months may experience a period of renewed activity after an operation unrelated to the arthritis. Furthermore, postoperative arthritis may complicate various surgical procedures in persons who never have had difficulties in the joints before, but in our experience the prognosis is not, as a rule, serious. The rather mild subacute condition seems to burn out rapidly. Such complications are largely confined to the winter season.

Endocrine factors.—Gross alterations of activity of the thyroid gland (hypothyroid or hyperthyroid states; thyroidectomy) seem to be associated occasionally with recrudescences in arthritis. Occasionally the onset of infectious arthritis follows thyroidectomy within a few weeks. After removal of the gland previously existing arthritis may be unfavorably influenced. Pains in joints and muscles are common symptoms in myxedema, and the administration of preparations from the thyroid gland almost always increases the pain for a time, as indeed it does in arthritic patients without myxedema. In general, however, studies in basal metabolism in chronic infectious arthritis have not shown consistent or notable alterations.

The influence of alterations in ovarian and uterine activity

are much more common. Certain manifestations in the joints and skin seem to choose the age of puberty or the menopause as the time of their special appearance. Acne at puberty and icthyotic changes at the menopause are common, whereas the times of onset and cessation of menstruation seem particularly favorable for the institution of infectious arthritis. Others feel that that form of arthritis which we regard as a "static-senescent" form, which involves the weight-bearing joints of elderly obese patients at the menopause, is sufficiently related to the cessation of the menses to be called "climacteric" or "menopause" arthritis.

The brief series of cases reported reflects our larger experience regarding the aggravating influence of the menses. Some patients do not note any change in symptoms in the joints during this period; others note increasing disability (stiffness and pain with or without increase in swelling and redness) just before, during, or just after the menstrual period. Some patients experience an annoying exacerbation which may continue for several days; others note a rapid, diphasic phenomenon similar to that resulting from treatment with protein. That is, the exacerbation is only transient, and after a few hours or a day or two is followed by an increased sense of well-being. Nor does the actual menstrual flow seem necessary. A few women have a definite, more or less regular, intermenstrual period (mid-monthly) of increased disability. In one case a patient who was accustomed to marking the calendar noted a continuation of monthly exacerbations for many months after the menopause and before the possible endocrine influence stopped. One of us (Hench) has expressed the belief that exacerbations associated with the menses do not necessarily denote pelvic infection, but that they may be the result of physiochemical alterations attending the menstrual cycle.

Three alterations that occur during the menses suggest themselves as possibly underlying these recrudescences: (1) changes in basal metabolism; (2) circulatory changes, among them alterations in cardiac output (diminution), and (3) alterations in the threshold of irritability. Any of these might afford an explanation, but the bodily changes associated with the menses

are so numerous that selection is speculative. As Petersen and Llewellyn have suggested, the menses are one of a variety of biologic alterations that may propagate reactions similar to those induced by foreign protein; they represent only one expression of the biologic rhythm that may predispose, precipitate, or aggravate the symptoms in the joints in the syndrome called arthritis.

Pregnancy also exerts a variable influence. At times its onset improves markedly the symptoms and signs of arthritis. In other instances its conclusion initiates, or is associated with, a recrudescence of the disease. This series includes only four patients who had associated pregnancy. Two patients experienced miscarriages without additional involvement of the joints. Two patients completed their pregnancies; one patient felt better throughout the entire period, whereas one had increased pain during the last three months, but felt much better afterward. The latter felt that her increased difficulties were largely static, confined to the weight-bearing joints.

The remaining factors.—The rôle and possible explanation of the action of the remaining factors cannot be considered in detail. Some factors (irregular sleep, worry, lack of sunshine and fresh air, and chronic invalidism) belong with the influences which lower nonspecific resistance. In this small series there were either no experiences with, or no unfavorable influences noted from, diets high in fat (milk, butter, and cheese), from diarrhea, mental fatigue, or worry, varicose veins, and radium or roentgen-ray treatment. These are factors noted by others as being occasionally predisposing causes.

Summary of decompensating factors.—The four outstanding factors which, in the minds of the patients studied, were responsible for interruptions in therapeutic progress were physical excesses, phenomena of the weather, periods of constipation, and intercurrent infections. These and the others noted will sufficiently demonstrate the multiplicity of factors that may influence arthritis of whatever primary cause, but particularly infectious arthritis. These data lend meager support to the theory that there is a sole cause for inflammation in a given

joint, and emphasize again the ideas expressed by many authors regarding the need for the "enlarged etiologic outlook" on arthritis.

To explain the possible correlation in this multiplicity of factors of how arthritis can be precipitated or made worse in so many diverse ways, an adaptation of a formula [1] relative to infection, immunity, and resistance in general may be pertinent:

$$A\ (+ \text{ or } -) = \frac{O - N - S}{R}$$

The presence (+) or absence (−) of arthritis (*A*) does not depend only on the presence of an organism (*O*) in certain numbers (*N*) or of a certain virulence or specificity (*S*), but also on the counterbalancing factor of resistance (*R*). The components that make up resistance are, of course, legion. A few are: adequate specific and nonspecific immune bodies (opsonins, agglutinins, antibodies, ferments); sufficient erythrocytes and leukocytes; influences dependent on blood volume, blood sugar, and blood salts; reticulo-endothelial and lymphoid defense; the reserve function of all organs, and physical protection afforded by warmth, food, and so forth. Regarding the onset of arthritis, therefore, and the interrelation of infection and nonspecific predisposing factors, it seems graphically clear that the numerator (focal infection) may be unchanged at a given time and yet arthritis may be precipitated from that focus because of the alterations in the value of the denominator (the resistance of the patient). Many of the aggravating factors also act on the denominator, reducing resistance rather than increasing the numerator (the specific infection). This lowering of resistance may be either of joints chiefly, such as that brought on by localized trauma, or of the body in general through the various factors noted.

The importance of the factor of resistance in determining prognosis may be illustrated by the following experience of one of our patients. She and her mother and brother all had influenza in 1918, following which all had chronic infectious

[1] This formula is a modification of one used by Theobald Smith.

arthritis. The brother, although seriously crippled for a year, eventually made an excellent recovery with little residual disablement. The mother almost at the onset became confined to bed, experienced a progressively incapacitating arthritis during a period of six years and died of "the arthritic infection and exhaustion." The patient herself, on the other hand, has struggled for eleven years with a progressive infectious arthritis which, although never confining her to bed, she has never been able to relieve.

PREVENTION OF EXACERBATIONS

Methods of prevention and treatment of exacerbations are identical with methods of prevention and treatment of the disease itself. In order to prevent exacerbations it is necessary to rely not only on adequate removal of the focal and disseminated infection in the joints, but also to promote an increase of nonspecific and specific resistance by nonspecific and specific vaccines and by all those general hygienic measures included in that vague prescription to the patient "common sense treatment," or "general measures to build up resistance."

Regardless of faithful continuation of available methods of treatment exacerbations may occur. Some exacerbations are preventable if adequate precautions are taken. Some exacerbations are not preventable, for the determinants are outside of the patient's control, for example, climatic variations, menses, and some intercurrent infections. The patient's program should be outlined to avoid the influences of the former, and the morale should be protected to survive the discouragements induced by the latter. The patient should anticipate the possibility of an interrupted type of recovery and persevere in treatment in spite of this.

Some specific suggestions for patients might be laid down in the form of a prescription, as follows:

1. Avoid physical excess. Modify physical expenditure to suit compensation of joints. Carefully find the limits of joint tolerance for work and for physiotherapy and stay just below, but not much below, these limits. As joint tolerance will vary,

depending on other factors, increase or decrease activity of the joints. At first extend the limits of tolerance of the joints to activity by no weight-bearing exercises rather than by weight-bearing exercises. This gives maximal functional stimulation with minimal trauma.

2. Avoid constipation. Three diets are suggested: (*a*) a high-residue diet, of 800 gm. bulk; (*b*) if sensitive to a high-residue diet, employ a moderate residue-diet of 500 gm. bulk and 300 gm. fruit juice, or (*c*) if neither of the former are successfully tolerated, a low-residue diet high in fat.

3. Special dietary prescriptions are not generally indicated. If idiosyncrasy to any carbohydrates or proteins in particular or in general is repeatedly demonstrated, or if an intake high in calories causes trouble, avoid this particular or general excess.

4. Mental worry from unrelated sources is an outside problem which should be corrected as far as possible. If the worry is from arthritic disability, the optimism derived from the benefit of consistent treatment may minimize such worries.

5. Avoid postural difficulties, cramped postures, and so forth, as much as possible by having comfortable chairs and a comfortable bed, and by frequent activity, with alternating periods of rest for the joints.

6. Avoid climatic alterations as much as possible by (*a*) proper heating and ventilation of the house; by (*b*) proper clothing, sufficiently warm for winter and changeable weather; by (*c*) precautions if exposed to cold and damp, such as change of clothing and a hot, stimulating bath; by (*d*) antagonizing the reaction of a natural cold climate by periods of physiotherapy daily, but trying to find the optimal form or forms of physiotherapy; by (*e*) if necessary making the change to a warmer climate, and by (*f*) stimulating skin reactivity to changes in environment by contrast baths, douches, and so on.

7. Build up general resistance by (*a*) regular habits of sleeping and eating, and by (*b*) periods of exposure to natural physiotherapy as exemplified by fresh air, sunshine, a daily walk or ride.

So long as the exact causes and the mechanism of production of infectious arthritis are uncertain, there will be little specificity

in treatment of the disease either at its onset or in its exacerbations. One of the most significant alterations is the loss of adaptability of the joints, as well as of the whole organism, not only to abnormal irritants (infection, excessive trauma, senescence, and altered chemical constituents of the body), but also to the ordinary normal and physiologic processes of joint-motion and weight-bearing. Joints and their infections certainly do not live to themselves alone. Eventual success in building up their resistance, whatever that means, will consist in increasing and restoring to normal the patient's capacity for adapting his whole body, as well as his joints, to the mutations of his environment, with all its exigencies.

THE PROSTATE GLAND AS A FOCUS OF INFECTION IN ARTHRITIS

ALLEN C. NICKEL AND LOUIS G. STUHLER

ARTHRITIS, due to focal infection, is well known, as is also the association of the gonococcus with certain forms of arthritis. Of more recent knowledge is the idea that the prostate gland may be a focus of infection. In 1924, with Rosenow's advice, we began culturing prostatic secretions obtained by massage, by the methods he has used so successfully in other diseases, to determine whether the prostate gland harbored pathogenic organisms which would localize electively when injected intravenously into rabbits. We were hopeful of finding such organisms, since it is known clinically that repeated prostatic massage is of value to some patients who have arthritis. This idea became more promising when cultures of secretion from the prostate glands of patients with arthritis, attributed primarily to gonococci, did not contain gonococci, but instead practically pure cultures of green-producing streptococci. Some of the earliest results were reported by one of us at the annual meeting of The Society of American Bacteriologists in 1924, and reference to the problem has been made in subsequent papers. Von Lackum, and Holloway and Von Lackum also have emphasized the prostate gland as a focus of infection from a clinical standpoint.

At this time we would like to present the accumulated data obtained with cultures made from prostatic secretions in patients who had arthritis, the results obtained in rabbits by the injection of such cultures, and some of the results in patients following treatment for prostatitis. The method of obtaining the cultures has been described in previous publications.[1, 3, 4]

During the period from October, 1925, to October, 1929, we made cultures in approximately 400 cases of arthritis in which the prostate gland was suspected of being a focus of infection. The cultures were made as a routine in glucose-brain broth (with and without a top layer of petrolatum), in glucose-brain agar, and aërobically on a blood-agar plate. Approximately 32 per cent of the organisms, when first isolated, did not grow aërobically on a blood-agar plate, but grew well in glucose-brain broth, which provides a gradient of oxygen tension. Many of these strains would not grow aërobically on a blood-agar plate until first grown in glucose-brain broth. In the beginning cultures for gonococci were attempted also on suitable mediums in cases of chronic arthritis in each of which there was a history of gonorrhea, but we were not able to isolate that organism. Because of the quantity of the work, and repeated negative results, this phase of the work was abandoned later and the mediums were employed routinely, as has been mentioned.

RESULTS

The organisms isolated consisted of various Gram-positive cocci, diphtheroid organisms, and Gram-positive and Gram-negative bacilli. These organisms, when freshly isolated, were injected intravenously into rabbits. The average amount injected was 5.5 c.c., and this was repeated twice at intervals of from one to three days, with the use of freshly grown subcultures. In the investigation of each strain, each of two rabbits usually was given an injection. However, in some instances, only one rabbit was given an injection, either because of the scarcity of rabbits, or because of a desire to conserve rabbits in cases which were not promising. The average life of the rabbits that died was seven days, and of those that were anesthetized, eighteen days. Many of the rabbits were allowed to live until they showed signs of recovery or until they became markedly crippled because of the arthritis. In some instances the arthritis disappeared entirely, but was produced again by reinjection of the culture. We soon learned the futility of injecting Gram-negative bacilli of the colon group, since the

dosage ordinarily used killed the rabbits and smaller doses did not produce localization of organisms.

When arthritis developed in the rabbit the causative streptococcus could be isolated from the joint in pure culture. This was possible because the rabbit destroyed the other organisms which were nonpathogenic, but was not able to destroy the green-producing streptococci that produced the arthritis. Altogether 233 rabbits were given injections, and in ninety-five (43.7 per cent) lesions of the joints developed. Seventy-three of these 233 rabbits were given injections of nonpathogenic strains that did not produce any lesions. About a fifth of these nonpathogenic strains consisted mainly of streptococci, another fifth of staphylococci and sarcinæ, another fifth of bacilli, and the other two-fifths of mixtures of these organisms.

In order to evaluate the elective localizing power of the pathogenic streptococci, we eliminated from our figures these seventy-three rabbits which received injections of the various strains that did not produce any lesions. Thus, 160 rabbits were given injections with eighty-five strains pathogenic for rabbits. For the most part each strain was injected into two rabbits. Of the eighty-five strains, seventy-one (84 per cent) produced lesions of the joints in at least one of the rabbits which received an injection of a given strain. Of the 160 rabbits which were given injections, ninety-five (59 per cent) became affected with lesions of the joints, whereas lesions of the liver occurred in only 7 per cent, of the lung in 6 per cent, of the kidney in 4 per cent, of the muscles, gallbladder, stomach or duodenum in 3 per cent each, and of the bowel, appendix, eye, and heart in 1 per cent each.

Fifty-six control rabbits were given injections with cultures from prostate glands of patients without complaints of systemic disorders. According to the results no one particular place in the body was selected by these heterologous strains. Lesions of the joints occurred in eight (14 per cent) of the control rabbits; lesions of the muscles, liver, stomach, and duodenum, and lungs in five (9 per cent) each; lesions of the kidneys and bowel, in four (7 per cent) each; lesions of the appendix in three (5 per

cent); lesions of the gallbladder in two (4 per cent); and lesions of the skin in one rabbit (2 per cent). Thus, by comparison, in 59 per cent of the rabbits that received injections of pathogenic strains, lesions of the joints developed; in contrast similar lesions developed in only 14 per cent of the control rabbits.

CORRELATION OF FOCI

There were eighteen cases in which all possible foci were searched for and cultures were made. In four cases a focus was not discovered. Of the remaining fourteen, twelve had foci in the prostate gland. In two instances the prostate gland was not a focus, but the focus was found in the tonsils. In five cases the prostate gland was a focus, but foci were not found elsewhere. In seven cases in which the prostate gland was found to be a focus, the teeth also were foci in three cases, and the tonsils in four cases. That these foci are interrelated, or harbor the same microbes, is shown by the fact that the organisms isolated from the various foci in a given case produce arthritis when injected into rabbits, and the strains, on recovery from the affected joints, act similarly in the different sugar mediums.

The following report of a case illustrates the value of adequate treatment of all foci, especially of the prostate gland, when it is shown to be a focus.

A minister aged sixty-three years entered The Mayo Clinic in July, 1926, stating that he had had an attack of arthritis for the first time in 1891 and had remained well after that until 1913, when he had had a second attack. A year later he had had a third attack, which had confined him to bed for a week. The fourth attack had begun in March, 1926 and thereafter he had had pain in the back and neck. He also had had occasional attacks of neuritis since 1913, but during the last year they had become much worse and had involved, chiefly, the extremities.

General examination revealed a very lame, elderly man, with marked limitation of motion of the spinal column, hips, and shoulders. Tonsillectomy had been performed two years previously. A nasal polyp, three pulpless teeth, prostatitis graded 4, and marked nocturia were noted. Roentgenograms of the spinal column and sinuses gave negative results. Treatment of the prostate gland was advised after adequate treatment of the other foci. Consequently, a fistula of the antrum was cureted, the nasal polyp was re-

moved, and the three pulpless teeth were extracted. Cultures from the teeth consisted of green-producing streptococci which produced arthritis in rabbits when injected intravenously. Cultures of the prostate gland also consisted of green-producing streptococci.

These freshly isolated cultures of the prostate gland were injected intravenously into two rabbits; each received two daily injections, of 5 c.c. each, of a twenty-four-hour glucose-brain-broth culture. Three days later one of the rabbits favored its hind legs when hopping; on the sixth day the rabbit was found dead. The joints of both hind legs were enlarged, and the tissues about them were markedly hyperemic. There was seropurulent fluid in each knee joint. Cultures of the blood remained sterile, and those of the joints contained green-producing streptococci. Gross evidence of arthritis developed in the other rabbit on the fourth day. It refused to hop and acted as if it were trying to protect its legs. When at rest, the anterior part of the thorax and abdomen touched the floor, so as to remove the weight of the body from the legs. The animal lived six days. Necropsy revealed enlarged

FIG. 240.—Arthritis of the elbow and wrist of a rabbit six days after conclusion of a series of two daily injections of 5 c.c. each of a freshly grown culture in glucose-brain broth of streptococci obtained from the prostatic secretion of a patient with arthritis.

knees and an enlarged right wrist and right elbow. Seropurulent fluid was obtained from all the affected joints. Cultures of the blood contained a Gram-negative bacillus, whereas a green-producing streptococcus was isolated from the affected joints (Fig. 240). Figure 241 is a section of the tissues of the joint shown in Figure 240, and illustrates the infiltration of the tissues with numerous leukocytes and some round cells, especially adjacent to the smaller blood vessels. Figure 242 shows the streptococci scattered throughout the tissue shown in Figure 241.

The patient remained for treatment, by massage and instillations, of the prostate gland, and the joints were treated with light and heat. One month later the patient was "much improved clinically and the prostatitis 75 per cent improved." The patient went home supplied with an autogenous

vaccine made from the strain isolated from the rabbit's joints; this was to be used only if his condition became worse. Two months later he returned for reëxamination and stated that he had continued with the prostatic treat-

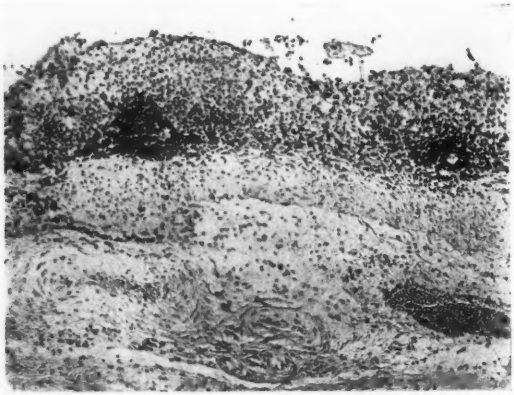

FIG. 241.—Section of the tissue of the elbow shown in Figure 240, with marked edema of the capsular tissue and with cellular infiltration, especially surrounding the two smaller blood vessels (hematoxylin and eosin × 90).

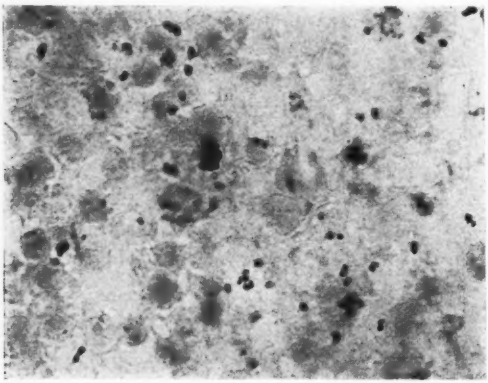

FIG. 242.—Streptococci present in the cellular infiltration shown in Figure 241 (Gram-Weigert stain × 1000).

ment and was feeling much better. He was dismissed, but was advised to continue the prostatic treatment. One year later he again returned feeling "considerably improved." Evidence of prostatitis could not be elicited

even under provocative treatment. The patient returned again in February, 1929 (one and a third years later). General examination at that time did not reveal prostatitis. He has had "no further rheumatic pain" and it has never been necessary for him to use the autogenous vaccine.

The following report of a case illustrates how difficult it sometimes is to eradicate a focus in the prostate gland, and also demonstrates the value of treatment by vaccine.

A man aged twenty-two years entered The Mayo Clinic in June, 1924. He had had arthritis of the left hip since childhood. Two and a half years before he came to the clinic the pain in the hip began again, and there was stiffness also in the other joints of the body, especially in the shoulders, neck, and back.

General examination revealed a tall, asthenic young man who walked with difficulty. There was definite limitation of motion of the shoulders and hips. A roentgenogram revealed hypertrophic arthritis of the upper lumbar and sacro-iliac joints. The tonsils had been removed elsewhere. Prostatitis graded 3 was present. The prostate gland was treated locally for two months and injections of solution of lactalbumin (Aolan) also were given. At the end of this time the patient's condition had improved and he was dismissed.

The patient returned after nine months and stated that he had continued to improve until he had contracted influenza, when the arthritis had become much worse. Since then his recovery had been tedious. The prostate gland was treated again for about seven weeks, after which he had felt very well, and he was again dismissed in August, 1925. He returned in October, 1927, stating that he had improved up to June, 1927, when he had suffered a relapse. Examination revealed residual prostatitis graded 3, and one pulpless tooth. Cultures were made from the prostate gland at this time and green-producing streptococci were found. The pulpless tooth was extracted.

One rabbit was injected with a culture in glucose-brain broth of freshly isolated streptococci obtained from the prostatic secretion. Seropurulent arthritis of both knees developed and crippled the animal so that it was not able to hop. The animal was chloroformed twelve days after injection. Necropsy revealed enlarged knees, which contained seropurulent material, and cultures therefrom consisted of green-producing streptococci. Two rabbits were given injections of freshly isolated cultures of the apex of the extracted tooth. They were given three daily injections of 6, 7, and 8 c.c., respectively. Clinical symptoms of arthritis developed in both rabbits, such as increased warmth and enlargement of the joints which the animals favored when hopping. One rabbit was chloroformed one week after the first injection and necropsy revealed seropurulent arthritis of the right knee-joint. Cultures of this joint consisted of green-producing streptococci. Cultures of the blood remained sterile. The other rabbit was chloroformed twelve days after the first injection. Necropsy revealed similar arthritis of both knee-joints, and also of the right shoulder. Cultures of the affected joints yielded streptococci, while cultures of the blood remained sterile.

Because of this selective action of the organisms an autogenous vaccine was made from the strains recovered from the joints of the rabbits. The patient was again dismissed after a month of local treatment of the prostate gland and injection of the autogenous vaccine. He was advised to continue the treatment of the prostate gland as well as the treatment by vaccine. A letter received from him in February, 1928 stated that he was "feeling fine, with the exception of a slight flare-up following a cold," and that the treatment by vaccine seemed to be very beneficial. A letter received from his home physician in December, 1928 stated that the patient's arthritic condition was much improved, but that it had not entirely cleared up.

COMMENT

The prostate gland apparently is a focus of infection in certain cases of arthritis, but, as a general rule, it is not a focus as often as are the other potential structures, such as tonsils, teeth, and sinuses.

In this group of 400 cultures seventy-one contained organisms with affinity for the joints. Had we obtained a culture of the prostate gland from every male patient with arthritis the percentage of positive cultures no doubt would have been even less. On the other hand, in five cases the prostate gland was found to be a focus when foci were not found elsewhere. This apparent preëminence of the prostate gland may be partly explained by the fact that other foci of infection had been removed before the patient came to The Mayo Clinic, but the prostate gland, as a focus, had passed unrecognized.

The causative organism was usually a green-producing streptococcus, although in a few instances it was a Gram-positive coccus resembling *Staphylococcus albus*, proved to be pathogenic since it produced arthritis and was isolated in pure culture from the joint. This organism may be similar to the staphylococcus-like organism reported by Crowe, and which he believes has significance in arthritis.

Because it is usually impossible to recover gonococci from the infected prostate glands of patients who have had chronic gonorrheal arthritis and because, instead, a streptococcus with affinity for the joints of rabbits usually is recovered in such cases, it seems likely that continuance of the arthritis in such patients may be due to the streptococcus rather than to gono-

cocci. Further evidence to this effect is the marked improvement sometimes noted when an autogenous vaccine made from this streptococcus is used as part of the treatment. It is possible that the prostate gland infected primarily with the gonococcus is the primary focus which becomes infected later with the streptococcus. The prostate gland may be considered as a secondary focus in those cases of nongonorrheal arthritis in which removal of other foci has brought about only temporary relief, but in which subsequent adequate treatment of the prostatic infection has permanently bettered the patient's general condition.

In any event the prostate gland has been found to be a definite focus of infection often enough to warrant its consideration as a possible focus in any male patient with arthritis.

CONCLUSIONS

Cultures of the prostate gland from patients with arthritis often contain green-producing streptococci which have selective affinity for the joints of experimental animals when injected intravenously. Adequate local treatment of the prostate gland so infected, sometimes with the use of an autogenous vaccine, often improves the general condition of patients, especially if the other foci also have been properly treated.

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FURTHER RESULTS OF SYMPATHETIC GANGLIONECTOMY AND RAMISECTOMY IN CHRONIC INFECTIOUS ARTHRITIS

JOSEPH G. MAYO, ALFRED W. ADSON, AND LEONARD G. ROWNTREE

DURING the last three and a half years fourteen operations of sympathetic ganglionectomy and ramisectomy have been performed in thirteen cases of chronic infectious arthritis. The results in the first case have been fully described, and brief reports of several other cases have appeared in the Proceedings of the Staff Meetings of The Mayo Clinic. We now wish to present the results in the ninth case in the series which was studied in the clinic.

The patient, a physician aged thirty-two years, had been in private practice one year when arthritis developed. Two years before examination, while playing baseball, he noticed for the first time pain, swelling, and stiffness in the palm of the left hand in the region of the first metacarpal bone. This was followed by involvement of the spinal column especially in the cervical region, the right shoulder, the left knee, both feet, and ankles, and the wrists and hands. The course was irregularly febrile, the temperature ranging from 99° to 101° F. for several months. He had tried many forms of treatment without avail and came to the clinic in September, 1929, after having spent ten months in bed.

General examination revealed a man, prematurely aged, considerably underweight (about 30 pounds). He looked pale, tired, and somewhat haggard from pain and loss of sleep. He was bedridden and was unable to walk. Practically all of his joints were affected by the arthritis. There was rather marked spondylitis, with considerable tenderness over the cervical portion of the spinal column and a somewhat less degree of tenderness over the lumbar region. Rotation of the neck was markedly limited. Flexion and extension were also limited, but to a slightly less degree. Motion of the thoracic portion of the spinal column was about 60 per cent of normal, and that of the lumbar portion about 20 per cent of normal. There was tenderness over the condyles of the jaw. The shoulders were involved, especially the right one, and there was considerable limitation of abduction. The right elbow extended to 165 degrees and flexed to 60 degrees. The left elbow was free. The wrists were puffy, stiff, and painful, the right more than the left. All the fingers

were swollen and painful, particularly the first row of interphalangeal joints. Motion in the fingers was considerably limited. The hips were relatively free of involvement. Both knees were swollen, graded 2 to 3; the left knee was more swollen than the right. The right knee could be flexed 45 degrees and the left 20 degrees. The left knee was stiff and extremely painful on motion. The ankles were also stiff and painful, the left was practically ankylosed and the right had only 20 per cent motion. There was striking swelling of the ankles and feet; graded 4. The extremities were cold, clammy, and sweaty to the touch. Perspiration in the feet was extreme. It appeared as a diffuse mist at times; again it appeared as beads of sweat which coalesced and formed drops. The sheet under the heels almost invariably presented two large wet areas soaked with sweat. The arthritis was of the periarticular type which was confirmed by roentgenograms of many joints. The laboratory tests revealed little of interest aside from low-grade secondary anemia, in which the hemoglobin was disproportionately reduced. The hemoglobin was 50 per cent; the erythrocytes numbered 4,800,000 and the leukocytes 7,800. Urinalysis and the Wassermann reaction of the blood were negative. Roentgenologic examination of the sinuses, teeth, gallbladder, and intestine gave negative results. There was no evidence of infection in the mouth or nasopharynx. The tonsils had been cleanly removed elsewhere several years previously. The prostate gland gave but slight evidence of infection.

Typhoid vaccine and treatment by physiotherapy were given for ten days, with little, if any, benefit. The vascular index of the feet was determined and was found to be high. Owing to the extreme sweating, the marked swelling, the coldness, and clamminess of the extremities, the periarticular nature of the arthritis, the height of the vascular index, and the lack of arthritis in the hips, it was felt that the patient was an ideal subject for lumbar sympathetic ganglionectomy and ramisectomy. The patient also felt that further medical treatment offered little if anything, and expressed his desire to undergo the operation immediately.

Bilateral lumbar sympathetic ganglionectomy and ramisectomy were done October 1, 1929. Convalescence following the operation was uneventful save for the unmasking of perineal neuritis. The effects of the operation on the lower extremities were striking. The left ankle, which had been apparently ankylosed, became movable within a few hours. The right ankle and both knees could be moved freely and without pain. The skin of the feet and legs became warm, dry, and pink by the time the patient had returned from the operating room. The swelling of the feet, which was pronounced prior to operation, rapidly disappeared during the next few days. The legs and feet felt warm and comfortable. He said they did not feel like his own feet, and on beginning to walk he said it seemed impossible that they really belonged to him. Within two weeks after operation his general appearance changed materially. He looked rested, free from pain and much fresher, even younger. For about eight days the joints were almost entirely free from pain and the motility was greatly increased. This is a phenomenon which frequently has been witnessed after operation, and in many cases involves all the extremities irrespective of whether or not their sympathetic control has been released. Although there was marked and increasing relief

of pain, lessening of swelling and increase in mobility while the patient was in bed, improvement was not so pronounced when he began to walk. The change in progress of course was due to the trauma incident to walking. However, as the patient slowly increased his activities the discomfort disappeared and by the time he was dismissed, he was able to walk unassisted.

Neurologic examination disclosed reflex atrophy. It was found that the patient had had a point of tenderness behind the neck of the fibula on the left for six to eight months, and that beginning three days after operation, a peculiar sensation had appeared over the dorsum of the left foot and slightly up the anterior lateral surface of the left leg. There was limited motion in the left toe dorsally, but power seemed weaker than on the right; pain prevented testing. The common perineal nerve was very tender near the head of the fibula and there was referred pain down the foot. It was obvious that perineal neuritis had developed from mild pressure.

Active and passive motion by physiotherapy were started in the lower extremities before walking or bearing of weight was allowed. On the thirtieth day after operation, the patient walked for the first time, most of his weight being supported in the walker. The amount of walking was gradually increased each day as his strength and confidence increased. He quickly graduated from the walker to crutches and then to the use of canes. November 16, forty-six days after operation, he returned home; he walked by the help of canes.

A report received December 1, two months after operation, indicates that the condition was much as it was when he was dismissed from observation. He had a better appetite and slept better. The feet were swelling less and the burning of the feet was diminishing. The desquamation continued. He was walking with the aid of crutches. He said that weakness of the knees and arches prevented rapid increase of the distance. There was no pain in the feet when walking, but there was slight pain in the left knee.

Several features of this case are of unusual interest. A study of the pulse and blood pressure with passive postural change was made. Studies just prior to operation showed a normal response when the pain and effort of standing were taken into consideration. Repetition of the studies five weeks after operation did not show deviation from normal.

Histamine studies were carried out on this patient after operation in both the upper and lower extremities. The results showed normal reactions in both areas following the intradermal injection of histamine.

The changes in the skin of the lower extremities following sympathetic ganglionectomy, which have been observed in all our cases, were definite and striking. They started within a few hours after the operation. The skin, which prior to operation had been pale, cyanotic, and sweaty, became dry, warm, and pink. An ichthyotic appearance was noted in a few days and later desquamation. We have seen this in other cases. As a rule fine, flaky scales are detached during desquamation. This persists for a number of weeks and eventually disappears. The nails which before operation exhibit trophic changes, also undergo metamorphosis, grow more rapidly, and assume a strictly normal appearance. In this particular case there was an area of slight sweating after sympathetic ganglionectomy in the region of the internal

malleolus. This is unique in our experience. However, in this area there were pigmentation and evidence of burning from previous treatment by light.

The results in this case at the time the patient was dismissed were considered entirely satisfactory; the complicating perineal neuritis persisted, although it was improved considerably. There is a striking difference in the rate at which different patients respond to sympathetic ganglionectomy and also in the rate of improvement in different joints in the same patient. The most striking effects are seen peripherally first in the hands and feet. Later, and to a somewhat less degree, there is relief in the knees and elbows, and still later there is relief of pain, but to a considerably less degree, in the hips and shoulders. Arthritic joints with bony involvement respond to some extent, but neither so markedly nor so promptly as do the periarticular structures. The will to get well and courage are of considerable importance after sympathetic ganglionectomy, as in all other methods of treatment of arthritis. Bearing of weight is an important consideration in relation to pain, to the use of the joints, and to recovery after operation. Obese and heavy individuals have a considerable handicap in getting back the use of the lower extremities.

This case represents only a fair result for the first two months. The perineal neuritis unquestionably retarded progress to some extent. This is the only case in our experience in which this complication has been observed. Its origin cannot be determined. In all probability it existed before operation for about six months, but was masked by the presence of arthritic pain. However, the improvement during the first eight weeks holds out hope for the complete relief of the arthritis in the lower extremities.

DEFORMITY FROM FATTY ATROPHY IN THE ARM OCCASIONED BY INJECTIONS OF PITUITRIN IN CASES OF DIABETES INSIPIDUS

JOHN W. HARMEIER AND WILLIAM P. FINNEY

A peculiar form of local fatty atrophy in the subcutaneous tissues following repeated injections of insulin, has been described in the literature. A similar condition exists in narcotic addicts. We have noted the reaction following injections of pituitrin. Our first case was reported in the Proceedings of the Staff Meetings of The Mayo Clinic.[3] Recently two such patients have been observed at the clinic. The cases are reported herewith.

Case I.—A married woman aged fifty years who was first admitted to the clinic in October, 1924, complained of extreme thirst of about three years' duration. There was a history of syphilitic infection nineteen years previously. In 1922 the Wassermann reaction of the blood had been found to be positive, and she had received a course of mercury and arsphenamine. Her symptoms seemed to have begun with a severe headache which had lasted, off and on, for two weeks. Following this attack, marked polydipsia and polyuria had developed. At the time of the patient's admission, she was drinking approximately 12 liters of water a day. Her appetite was enormous. There was marked dyspnea on exertion.

Apart from obesity, nothing abnormal was found on general examination. The Wassermann reaction on the blood and spinal fluid were positive, otherwise the examination was essentially negative. The patient received 1 c.c. of pituitrin hypodermically each day during her stay in the hospital. The fluid intake was reduced to 2 to 3 liters of water a day. Following antisyphilitic treatment for five months she continued to take 1 c.c. of pituitrin twice daily.

In May, 1929, the patient returned for further antisyphilitic treatment. The intake of fluid, despite the use of pituitrin, had remained from 3 to 5 liters a day during the interval of four years. On the lateral aspect of each upper arm, where she had been giving herself hypodermic injections of pituitrin, were areas of marked reduction of adipose tissue, which produced deep de-

pressions. Hard nodules were palpable at the bases of these depressions. One of the nodules was removed for biopsy, and microscopically a foreign body reaction, with terminal fibrosis, was demonstrated. At this time the administration of pituitrin by nasal spray was tried and the intake of fluid was reduced to 2 to 4.5 liters a day. If pituitrin was omitted, almost twice this amount of fluid was taken.

Case II.—A young married woman aged twenty-five years registered at the clinic, August 19, 1929. Her reason for coming to the clinic was that she had heard of cases of diabetes insipidus being treated with intranasal spray. She said she had known for one and a half years that she had diabetes insipidus. When questioned about the onset and related incidents, she told of a fright which occurred prior to the onset of her present condition. One night she was visiting about a block away from home when suddenly the bell of a fire engine was heard. Immediately the safety of her home was feared, and she started out to investigate. On reaching the street she was informed that her house was on fire. When she neared her home, however, she discovered that this was not true. About a week later she noticed suddenly, one morning at eleven o'clock, an excessive thirst. The drinking of great quantities of water and polyuria followed. She had noticed polyuria two to three times on the night preceding the onset of thirst. Coincidental with this she noticed that she became fatigued, lost her appetite, and was losing weight rapidly. She estimated the intake of fluid as 8 liters a day and the same amount at night. One week after the onset she went to a sanatorium. In the course of a week after admission, a spinal puncture was made. This was followed by severe headache, generalized aching and nausea and vomiting, which gradually cleared up after about three weeks. The spinal fluid was normal on this examination. The patient then went home and her physician started pituitrin hypodermically. The dose was 1 ampule, and each dose was followed by cramps. The treatment enabled her to rest at night however, and she began to gain weight (35 pounds) and strength. Daily treatment with pituitrin hypodermically was given for three months before she came to the clinic.

At the time of admission the patient was taking water three times during the night. The quantity at night, before admission, was 3,600 c.c. from 8.00 p.m. to 8.00 a.m. Menstruation had stopped one year previously, but at the time of periods she had noticed some of the associated nervous phenomena. She had not been pregnant during her eight years of married life. Examination revealed definite subcutaneous atrophy of the right arm at the points where pituitrin had been injected (Fig. 243). Laboratory examinations were essentially negative. The intranasal spray of pituitrin, 1 ampule a day, was given. The administration of this was spread out through the day. The results were striking. On five successive days the results were as follows: the intake on the two days immediately preceding treatment was 11,350 and 10,550 c.c. respectively, and the output was 10,250 and 8,800 c.c., respectively. The intake on the first three days of treatment by 1 ampule of pituitrin was 8,200, 3,000, and 2,850 c.c., respectively, and the output was 8,100, 2,800, and 3,200 c.c., respectively. This shows a definite decrease in

both intake and output, and demonstrates the control effected by the intranasal administration of pituitrin.

FIG. 243.—Deformity of the arm caused by injections of pituitrin.

Following the experimental injection of insulin in rabbits, signs of degenerative changes are not observed in the connective-tissue cells of the panniculus adiposus, but these cells are widely separated by a mucigenous fluid, which produces the localized

edema seen following injection. Lawrence found that after frequent injections of insulin sections of the skin showed infiltration in the region of the vessels by lymphocytes and histiocytes, with some plasma cells and eosinophils. Three years after the injections were discontinued there were, also, fibrous strands passing down from the corneum and dividing the fat into coarse lobules. In Case I the biopsy demonstrated a microscopic picture essentially that of foreign body reaction with terminal fibrosis.

Two other factors were investigated in regard to insulin, namely, the possibility of a fat-splitting enzyme in the insulin, derived from the pancreas, and the question of sterilization of the hypodermic needle. The first question was ruled out by Rabinowitch after numerous experiments, and the second after he had considered the diversity of methods employed by patients.

Avery concluded that the injection of insulin or other substances injures the delicate protoplasmic-cell envelope of the fat cells, allowing the fat globules to be released. The globules, acting as foreign bodies in the tissues, result in the formation or histiocytes which take on lipophagic activity. Repetition of this trauma results in fatty atrophy at the site of trauma; that the reaction is nonspecific has also been proved from the fact that trauma from several types of injection gives the same picture.

It seems likely that the condition described is a nonspecific form of fatty atrophy resulting in deformity in the contour of the arm, which is caused by repeated trauma to the panniculus adiposus with subsequent lipophagic action.

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PHYTOBEZOAR. REPORT OF A CASE

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A MAN aged thirty-seven years came to the clinic first in October, 1923, for a general examination. He did not have any specific complaint except that he was somewhat nervous. He was the editor of a metropolitan newspaper in the South, and he was working strenuously ten or more hours a day which he thought caused his nervousness. He also gave a history of occasional attacks of epigastric distress associated with dizziness and "gas on the stomach."

On general examination, a moderate amount of periapical dental infection, large cryptic tonsils which contained large plugs of pus, and a noninflamed, draining postanal dermoid were found. Roentgenologic examination of the stomach was negative and gastric analysis one hour after a test meal showed total acidity 54, and free acidity 36; the quantity of gastric content was 80 c.c. It was thought that the patient's symptoms were due to overwork, with the possibility that his digestive disturbances were caused reflexly by chronic disease of the gallbladder or by chronic appendicitis. The postanal dermoid did not cause much discomfort, so he did not have it excised.

The patient returned to the clinic in July, 1925, with the complaint of stomach trouble which had started with diarrhea in January, 1924. The diarrhea had consisted of three to six watery stools a day with some blood at times, and had continued intermittently for six months. It was then replaced by a sense of fulness and vague distress in the epigastrium which appeared immediately after eating. Fatty foods were avoided because they produced the greatest distress. At times there also had been some pain in the epigastrium three to four hours after meals. There had been no nausea or vomiting, and soda did not relieve the pain. The results of general examination were essentially the same as on the first visit except that the postanal dermoid was not draining. Parasites or ova were not found in the stools. Roentgen-ray examination of the gallbladder with the dye test disclosed stones. Cholecystectomy was advised, but business duties prevented the patient's remaining for it.

In October, 1929 the patient came to the clinic for the third time. In 1926 during a prolonged attack of acute colicky pains in the abdomen associated with jaundice, he had been operated on elsewhere. According to his statement, a stone was removed from the cystic duct and all except a third of the gallbladder was removed. The remaining third was "everted and sewed to the liver." Since then he had not had colicky pains but at times had some stinging pains in the region of the gallbladder. Except for occasional spells of nausea, he had been well until the spring of 1929, when he

had an attack of nausea associated with vague distress under the left costal margin in the epigastrium; this had persisted for several weeks. He did not vomit during this attack. Since then he had been troubled considerably with nausea which was present on awakening in the morning and persisted until noon. It prevented him from eating breakfast, which he postponed until about 11.00 a.m. when the nausea had abated somewhat. Bowel movements and the eating of food did not affect the nausea. If he ate at or after midnight, he would not be nauseated in the morning. He had been somewhat constipated for several years and was taking laxatives frequently. His physical

FIG. 244.—Roentgenogram of the stomach showing displacement of the barium by the bezoar.

condition was essentially the same as on the previous visits except for some premature contractions of the heart. He was well nourished, appeared healthy, and there had been no loss in weight. The tonsils had not been removed and he still had some periapical dental infection. The electrocardiogram showed sinus arhythmia with some ventricular premature contractions. The results of a test meal now were: total acidity 32 and free acidity 16; the quantity of gastric content was 100 c.c. Roentgenologic examination showed what appeared to be a polypoid tumor in the lower end of the stomach which was considered operable (Fig. 244).

At operation two foreign bodies were found in the stomach which were removed through an anterior gastrotomy. There was no evidence of an ulcer of the stomach. Numerous adhesions were present in the region of the gallbladder, and the remnant of the gallbladder was not isolated. The common bile duct and the pancreas seemed normal by palpation. There were some adhesions in the lower part of the abdomen.

FIG. 245.—The persimmon bezoars removed at operation.

The foreign bodies were of a tarry black appearance, irregularly shaped, somewhat pliable, each 5 by 4 by 4 cm., and weighing together 32 gm. (Fig. 245). On sectioning they were found to consist essentially of a tan homogeneous material without accretion layers, in which were embedded skins and vegetable fibers. The patient stated that he ate a persimmon occasionally, but a friend with whom he played golf stated that whenever he missed him from the golf course he would find him in a persimmon tree.

COMMENT

Bezoar is a Persian term applied to concretions found in the stomach and intestines of animals. Bezoars were considered to have remarkable medicinal properties, especially as antidotes to poison. They are of several varieties, of which the trichobezoar, or hair ball, is the most common. The phytobezoar, or food ball, which was the kind removed in the case reported here, is composed of stems, seeds, skins, and fibers of fruits and vegetables.

The foods which have been found in phytobezoars include persimmons, prunes, salsify, and celery, along with detritus, such as starch granules, fat globules, and fatty acids. Persimmons have been found to form most of them, which is probably due to their high content of gum and pectin (14 and 7 per cent, respectively) which furnishes the cohesive material holding the seeds, vegetable fibers, and detritus together.

Only a few cases of phytobezoars were reported prior to 1923, when Hart reported six cases; since then a number of them have been reported.[1] Almost all the cases occurred among residents of the South where persimmons grow.

In most of the reported cases the symptoms began with an acute gastro-intestinal upset within a day or two after the ingestion of persimmons. In the present case the onset was not sudden and the patient did not associate it with the ingestion of persimmons. It is, therefore, impossible to determine how long the bezoars had been present, but they had probably been present six months or more.

The only symptoms in the case reported here were the intractable nausea in the morning when the stomach was empty and the associated pain under the left costal margin. With the absence of vomiting of blood, or decreased acidity in the gastric content, and of symptoms of pyloric obstruction, it was difficult preoperatively to fit the roentgenologic diagnosis of polypoid neoplasm into the clinical picture. In most of the cases of bezoars a correct diagnosis is not made preoperatively. Frequently neoplasm of the stomach is diagnosed preoperatively. The point reëmphasized by this case is that when a roentgenologic diagnosis of a tumor of the stomach is made in a case in which this diagnosis is not in harmony with the remainder of the clinical picture, a bezoar should be one of the things considered.

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PERIODIC EDEMA OF THE HAND WITH A SEVEN-DAY CYCLE; TREATMENT WITH HISTAMINE

SELMA C. MUELLER

ALTHOUGH angioneurotic edema is not an uncommon affection, edema appearing repeatedly in the same area of the body, and with a definite cycle of appearance and disappearance, is most unusual. There are few physiologic functions which occur at definite intervals, the menstrual cycle being the well-known example. Occasionally certain pathologic states associated with, or dependent on, menstruation assume the same periodicity. When, however, other bodily activities assume a cyclic character independently of any known physiologic cycle, they are observed with great interest.

Quincke, in his original description of acute circumscribed edema, mentioned the fact that, having once appeared, the swelling tends to recur in the same spots, at first irregularly, but later at regular intervals of about one week. Matas, in 1887, reported a definitely periodic case; the swelling occurred daily on the upper lip at 8 a.m., reached its maximum at 12 to 1 p.m., then gradually disappeared, to be entirely gone by 3 or 5 p.m. Matas also quoted Riehl as having cited a case with a fifteen-day cycle. Osler mentioned remarkable regularity in sequence of attacks, which may occur in cycles of seven, twelve, or fourteen days. Kermanner, Thost, and Goldschmidt reported isolated cases with fairly well-marked periodicity, and recently Weismann-Netter reported a case of periodic hydrarthrosis of the knee. In view of these rather scattered observations of the cyclic quality which circumscribed edema may assume, I wish to present a case of periodic edema of the hand, together with therapeutic results. The case presented here was reported at a meeting of the Staff of The Mayo Clinic, November 7, 1928, but at that time therapeutic results could not be recorded.

REPORT OF CASE

The patient was an unmarried Jewish woman aged twenty-nine years apparently in perfect health except for swelling which involved the entire left hand, and had existed for fifteen years. The swelling had occurred regularly on alternate Tuesday nights, so that when she awakened Wednesday morning the hand was swollen and painful. The swelling and discomfort would last one week and some time during the following Tuesday night would disappear entirely so that on Wednesday morning the hand was perfectly normal and remained so until the next Tuesday night. There

FIG. 246.—The hands during the period of swelling.

had been two periods of two years each during the last fifteen years when swelling had not occurred. The alternate periods of swelling and nonswelling had always been of one week's duration. There was no relation to menstrual periods, which, in fact, occurred much less regularly than the edema. A history of any dietary, psychic, or other influence which might cause the swelling could not be obtained. The patient had never seen any disease similar to her own, but knew of a man who had had intermittent hydrarthrosis of the knee-joint which occurred in a cycle of thirteen days. The patient had had injections of milk as a foreign protein before admission to the clinic, without benefit. Injections of pituitrin intracutaneously and subcutaneously were tried without benefit.

The result of general examination was essentially negative except for the moderate swelling of the left hand which occurred on alternate weeks, starting Tuesday nights. The swelling was never severe and extended up to the wrist. It was most marked over the dorsal pads of the second phalanges of the second, third, and fourth fingers, and less marked over the dorsum of the hand. The normal wrinkling of the skin was diminished on the left hand. The skin was somewhat shiny and indurated and more difficult to pick up than on the right hand. The hand was held in a position of slight flexion, and the fingers could not be completely extended or flexed because of pain. The color was not changed in the swollen hand, and the pulse and blood pressure were the same in the two hands (Fig. 246).

Surface temperature studies made with the electric thermocouple showed differences in temperature in the two hands. During the first period of swelling observed, the affected hand was warmer (1.9°) than the unaffected hand. During the period of nonswelling, the surface temperatures in the two hands were approximately the same. A comparison of the volume of the two hands during the period of edema showed that the affected hand displaced 5 to 30 c.c. more fluid than the unaffected hand. The hand was usually more swollen in the evening than during the early part of the day.

The swelling in this case was in many respects similar to the manifestations of cold allergy noted by Horton and Brown. Since histamine in minute doses had been used with some degree of success in some of these cases, it was decided to use it in this case. The treatment was begun with 0.02 mg. of histamine subcutaneously twice a day during the edema-free week. The dosage was gradually increased to 0.2 mg. twice a day during the first week. The first cycle of swelling after the beginning of treatment was not affected. In the hopes of obtaining results by continuing the treatment, the patient was given instructions to continue the treatment with her home physician over a long period of time. Dr. Joseph Brown, of Des Moines, Iowa, has very kindly kept us informed as to the patient's progress. The dosage was gradually increased and the cycle was broken very soon after the patient's arrival at home. Injections of histamine were continued; the injections were diminished to every second day, then to every fourth day, then to once a week, and finally, in April, 1929 (five months after treatment was started), they were discontinued. The patient remained free from edema until May. May 28, word was received that the edema had again appeared. More histamine was sent and Dr. Brown later reported that the cycle was again broken some time during June, since which time it has not recurred. The injections were given once a week until October, when they were discontinued.

Dr. Brown has used histamine in another case, that of a woman having had a continuous swelling of the left hand for six months. Ten days after the first injection the swelling subsided and had not reappeared at the last report.

COMMENT

Angioneurotic edema is considered by many authorities to be one of the bizarre manifestations of allergy. The allergy may apparently be due to various factors, such as foreign pro-

teins, and such physical agents as sunlight, heat and cold, trauma, and foci of infection. Lewis and Grant, from their extensive work on the vascular reactions of the skin to injury, concluded that the flush and subsequent edema of the urticarial wheals, pin-pricks, stroking, and burns of the skin are due to the release of diffusible substances from the skin by injury to tissue elements, causing dilatation of the vessels and increased permeability of the walls of the vessels. The flush produced is fundamentally the same as that which is produced by the introduction of histamine into the skin. Histamine itself was first recovered from the tissues of the body by Barger and Dale in 1910. Duke expressed the belief that allergic reactions may possibly be caused by absorption of histamine-like substances from the intestinal tract. Horton and Brown, in their report of six cases of cold allergy, stated that various studies had led them to believe that "a physical agent, such as cold, might break down certain molecules in the skin, subcutaneous tissues, or muscles, with the liberation of histamine or histamine-like bodies, which when carried into the general circulation would produce the typical histamine effects." If this is true, injection of increasing doses of histamine should induce refractory periods during which reactions will not occur. Since, in the case reported here, there was swelling which suggested the allergic type, it was decided to attempt to induce refractoriness.

Various other types of treatment for angioneurotic edema are mentioned in the literature. Among them are "desensitization" to specific foreign proteins, nonspecific foreign protein reactions, endocrine substances (especially thyroid and pituitrin substances), and various drugs, such as strychnine, and atropine; all of these varied forms of treatment have given questionable results. Psychotherapy succeeds in some neurotic cases. Histamine apparently has not been widely used for this purpose, since I have been able to find only one reference to its use in a similar case, that reported by Weismann-Netter in July, 1929; this was a case of periodic hydrarthosis relieved by subcutaneous injections of ergotamine tartrate.

SUMMARY

A case of periodic edema of the left hand occurring in a cycle of seven days is presented, together with the results of treatment by histamine. The histamine was given in increasing doses, and refractory periods were induced and maintained over long intervals of time.

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